8.1.3 Clinical adverse events (AEs) from the Phase II-III Tirofiban safety database (cont)

Next, the adverse events related to bleeding were summarized by the sponsor, and appear in the table below. The shaded boxes represents AEs where there is ≥2X difference between one of the two tirofiban groups and either its respective heparin group, or the total heparin group.

Table 8.1.3.2 Bleeding adverse events in the phase II-III trials of tirofiban from NDA 20-912".

| | Tirofiban + Heparin n=1953 | Heparin/ Procedures n=1887 | Tirofiban n=2032 | Heparin/ No Procedures n=1659 | Total Heparin[b] n=3546 |
|---|---|---|---|---|---|
| **Subjects with bleeding clinical AE** | 1021 (52.3%) | 733 (38.8%) | 424 (20.9%) | 143 (8.6%) | 876 (24.7%) |
| **Subjects without bleeding clinical AE** | 932 (47.7%) | 1154 (61.2%) | 1608 (79.1%) | 1516 (91.4%) | 2670 (75.2%) |
| **Body as a whole** | **1 (0.1%)** | **1 (0.1%)** | **10 (0.5%)** | **9 (0.5%)** | 10 (0.3%) |
| **Cardiovascular System** | 844 (43.2%) | 616 (32.6%) | 245 (12.1%) | 86 (5.2%) | 702 (19.8%) |
| Bleeding, postoperative | 659 (33.7%) | 468 (24.8%) | 139 (6.8%) | 34 (2.0%) | 502 (14.1%) |
| Extravasation | 8 (0.4%) | 3 (0.2%) | 13 (0.6%) | 4 (0.2%) | 7 (<0.1%) |
| Hematoma | 206 (10.5%) | 125 (6.6%) | 63 (3.1%) | 26 (1.6%) | 151 (4.2%) |
| Hemorrhage | 24 (1.2%) | 39 (2.1%) | 11 (0.5%) | 3 (0.2%) | 42 (1.2%) |
| Hemorrhage, IV site | 105 (5.4%) | 77 (4.1%) | 61 (3.0%) | 20 (1.2%) | 97 (2.7%) |
| **Digestive System** | 96 (4.9%) | 29 (1.5%) | 53 (2.6%) | 13( 0.8%) | 42 (1.2%) |
| Hematemesis | 17 (0.9%) | 6 (0.3%) | 4 (0.2%) | 0 (0.0%) | 6 (0.2%) |
| Hemorrhage, gastrointestinal | 18 (0.9%) | 4 (0.2%) | 11 (0.5%) | 6 (0.4%) | 10 (0.3%) |
| Hemorrhage, gingival | 19 (1.0%) | 3 (0.2%) | 11 (0.5%) | 3 (0.2%) | 6 (0.2%) |
| Hemorrhage, oral | 28 (1.4%) | 5 (0.3%) | 8 (0.4%) | 0 (0.0%) | 5 (0.2%) |
| **Hemic and Lymphatic System** | 4 (0.2%) | 1 (0.1%) | 5 (0.2%) | 0 (0.0%) | 1 (<0.1%) |
| **Respiratory System** | 125 (6.4%) | 33 (1.7%) | 143 (7.0%) | 21 (1.3%) | 54 (1.5%) |
| Epistaxis | 109 (5.6%) | 20 (1.1%) | 130 (6.4%) | 18 (1.1%) | 38 (1.1%) |
| Hemoptysis | 23 (1.2%) | 11 (0.6%) | 18 (0.9%) | 3 (0.2%) | 14 (0.4%) |
| **Skin and Skin Appendage** | 222 (11.4%) | 154 (8.2%) | 43 (2.1%) | 5 (0.3%) | 159 (4.5%) |
| Ecchymosis | 217 (11.1%) | 153 (8.1%) | 40 (2.0%) | 5 (0.3%) | 158 (4.5%) |
| **Special Senses** | 3 (0.2%) | 0 (0.0%) | 3 (0.1%) | 2 (0.1%) | 2 (<0.1%) |
| Urogenital | 73 (3.7%) | 49 (2.6%) | 29 (1.4%) | 18 (1.1%) | 67 (1.9%) |
| Hematuria | 67(3.4%) | 42 (2.2%) | 26 (1.3%) | 17 (1.0%) | 59 (1.7%) |

a. Data from NDA volume 1.2, Table C-39 and electronic datasets.
b. Includes all subjects from Heparin/ No procedures and Heparin/ Procedures groups.

8.1.4 Adverse Events Related to Laboratory Findings

8.1.4.1 Standard Analyses and Explorations of Laboratory Data

The collection of laboratory measurements was detailed in section 8.0.4.5 above. Of the three large phase III trials, PRISM and PRISM-PLUS collected lab data at least three time points following the start of study drug administration. In contrast, RESTORE trial collected only two sets of labs: one at baseline and one set 36 hours later. As a result, the incidence of detected lab abnormalities can be expected to be higher in the PRISM and PRISM-PLUS trials. In Phase II and Phase III, investigators were instructed to provide outcome for all adverse experiences, and it was expected that abnormal laboratory values would be followed through resolution. No specific follow-up criteria were outlined, however, for abnormal laboratory values.

8.1.4.2 Analyses Focused on Changes in Mean Laboratory Measurements

Analyses of mean changes in serum chemistries or hematology were performed for each of the phase III trials individually, but no summary analysis of the phase II-III database was performed. The results from the individual trials are reviewed below. Due to the size of the tables, only selected lab values which were of particular relevance (Hgb, Hct, platelet #, platelet count, ALT) or demonstrated potentially clinically significant change are displayed. The reader is referred to the original data in the NDA for further details. The number represent the mean change from the baseline value across all subjects with available data at the specified timepoint.

Overall, the mean hemoglobin and hematocrit fell in all groups, with the largest changes occurring in the tirofiban +heparin groups in the PRISM-PLUS and RESTORE trials. Mean platelet counts also fell, but the heparin alone group had the largest mean change. No other clinically significant changes in mean hematology or chemistry values were detected.

8.1.4.2 Analyses Focused on Changes in Mean Laboratory Measurements (cont)

PRISM-PLUS

Shown is the mean change from baseline at the specified time of measurement. Note that the number of subjects with available data decreases for the later time points. Hemoglobin and hematocrit fell in all groups, with the highest values in the tirofiban +heparin group. Mean platelet counts fell fastest in the heparin alone group. Mean ALT rose fastest in the tirofiban +heparin group.

Table 8.1.4.2. Abnormal and clinically significant changes in mean hematology values from the PRISM-PLUS trial".

| Lab adverse event | Tirofiban n=345 | Tirofiban +Heparin n=773 | Heparin n=797 |
|---|---|---|---|
| **Hemoglobin (g/dl)** | | | |
| 6 hours | -0.94 | -0.91 | -0.96 |
| 24 hours | -1.12 | -1.13 | -1.16 |
| 72 hours | -1.15 | -1.32 | -1.34 |
| 96 hours | -1.43 | -1.35 | -1.28 |
| 120 hours | -1.84 | -1.47 | -1.23 |
| Hematocrit (%) | | | |
| 6 hours | -2.8 | -2.6 | -2.8 |
| 24 hours | -3.1 | -3.0 | -3.2 |
| 72 hours | -3.3 | -3.8 | -4.0 |
| 96 hours | -4.1 | -4.0 | -3.9 |
| 120 hours | -5.5 | -4.3 | -3.9 |
| **WIC count ($10^3/mm^3$)** | | | |
| 24 hours | -0.22 | -0.33 | -0.42 |
| 72 hours | -0.28 | -0.52 | -0.69 |
| 120 hours | -0.18 | -0.50 | -0.87 |
| **Platelet count ($10^3/mm^3$)** | | | |
| 6 hours | -9.2 | -4.9 | -14.7 |
| 24 hours | -13.2 | -9.5 | -19.3 |
| 48 hours | -13.9 | -9.8 | -22.1 |
| 72 hours | -9.8 | -8.5 | -24.3 |
| 96 hours | -10.0 | -7.9 | -21.7 |
| 120 hours | -14.0 | -6.7 | -17.4 |
| Eosinophils (%) | | | |
| 24 hours | -0.03 | 0.32 | 0.36 |
| 72 hours | 0.83 | 0.33 | 0.62 |
| 120 hours | 0.44 | 0.68 | 0.64 |

a. Da from NDA volume 1.65, ref. 5, appendix 4.1.2.28.

Table 8.1.4.2.2 Abnormal and clinically significant changes in mean chemistry values from PRISM-PLUS".

| Lab adverse event | Tirofiban n=345 | Tirofiban +Heparin n=773 | Heparin n=797 |
|---|---|---|---|
| **Total Bilirubin (mgldl)** | | | |
| 24 hours | 0.07 | 0.00 | 0.00 |
| 72 hours | 0.02 | -0.05 | -0.03 |
| 120 hours | 0.01 | -0.05 | -0.04 |
| **BUN (mgldl)** | | | |
| 24 hours | -1.0 | -1.3 | -1.4 |
| 72 hours | -1.2 | -1.7 | -2.1 |
| 120 hours | 1.1 | -0.1 | -0.2 |
| **Creatinine (mgldl)** | | | |
| 24 hours | 0.04 | 0.02 | 0.01 |
| 72 hours | 0.02 | 0.03 | 0.03 |
| 120 hours | 0.06 | 0.09 | 0.10 |
| **ALT (U/L)** | | | |
| 24 hours | 0.1 | 0.9 | 1.0 |
| 72 hours | 2.4 | 6.7 | 6.4 |
| 120 hours | 5.3 | 21.3 | 18.5 |
| **Alkaline Phosphatase (U/l)** | | | |
| 24 hours | -3.3 | -3.9 | -4.3 |
| 72 hours | -2.4 | -3.2 | -3.8 |
| 120 hours | 4.7 | 2.7 | 0.4 |

a Data from NDA volume 1.65, ref. 5, appendix 4.1.2.28.

PRISM

The next two table summarize the change in the mean values for selected hematology and chemistry values from the PRISM trial. Note first that the mean change in hemoglobin/ hematocrit was roughly equivalent in the two groups. Mean platelet counts fell more quickly in the heparin arm. The heparin arm also had a higher mean change in serum ALT than the tirofiban arm.

Table 8.1.4.2.3 Abnormal and clinically significant changes in mean lab values from the PRISM trial".

| Lab adverse event | Tirofiban n=1616[b] | Heparin n=1616[b] |
|---|---|---|
| **Hemoglobin (g/dl)** | | |
| 6 hours | -0.78 | -0.71 |
| 24 hours | -0.69 | -0.70 |
| 48 hours | -0.67 | -0.74 |
| 72 hours | -0.69 | -0.67 |
| **Hematocrit (%)** | | |
| 6 hours | -2.2 | -2.0 |
| 24 hours | -2.0 | -2.0 |
| 72 hours | -1.9 | -2.1 |
| 96 hours | -2.0 | -1.9 |
| **WBC count ($10^3/mm^3$)** | | |
| 6 hours | 0.0 | 0.4 |
| 24 hours | -0.2 | -0.2 |
| 48 hours | -0.4 | -0.6 |
| 72 hours | - 0 . 1 | -0.5 |
| **Platelet count ($10^3/mm^3$)** | | |
| 6 hours | -6.4 | -9.7 |
| 24 hours | -7.6 | -12.6 |
| 48 hours | -4.9 | -13.2 |
| 72 hours | -7.2 | -10.5 |
| **Eosinophils (%)** | | |
| 24 hours | 0.34 | 0.47 |
| 48 hours | 0.61 | 0.71 |
| 72 hours | 0.74 | 0.67 |

a. Data from NDA volume 1.65, ref. 9, appendix 4.1.25.
b. The actual number of subjects with available data is lower than the number of subjects entered into the trial

Table 8.1.4.2.4 **A** ıormal and clinically significant changes in mean chemistry valuesfrom PRISM".

| Lab adverse event | Tirofiban n=1616[b] | Heparin n=1616[b] |
|---|---|---|
| **Total Bilirubin (mg/dl)** | | |
| 24 hours | 0.01 | -0.05 |
| 48 hours | -0.03 | -0.06 |
| 72 hours | -0.05 | -0.04 |
| **BUN (mg/dl)** | | |
| 24 hours | -0.8 | -0.8 |
| 48 hours | -1.0 | -1.3 |
| 72 hours | 0.5 | -0.1 |
| **Creatinine (mg/dl)** | | |
| 24 hours | 0.02 | 0.03 |
| 48 hours | 0.02 | 0.04 |
| 72 hours | 0.05 | 0.07 |
| **ALT (U/L)** | | |
| 24 hours | 0.42 | 0.54 |
| 48 hours | 0.86 | 1.18 |
| 72 hours | 1.64 | 6.87 |
| **Alkaline Phosphatase (U/l)** | | |
| 24 hours | -2.7 | -2.4 |
| 48 hours | -2.2 | -2.0 |
| 72 hours | -0.4 | -0.5 |

a. Data from NDA volume 1.65, ref. 9, appendix 4.1.25.
b. The actual number of subjects with available data is lower than **the** number of subjects entered into the trial.

**RESTORE**

The next two table summarize the mean changes **from** baseline for the subjects in the RESTORE trial with available data. There was a larger drop in both mean hemoglobin and mean hematocrit in the tirofiban (+heparin) group. There was a larger drop in the mean platelet count in the placebo (+heparin) group. Remember that the placebo group received significantly more heparin than the tirofiban group in the RESTORE trial (see table 6.2.3.12.2.1). Note that in both groups, the mean ALT tended to rise between O-36 hours.

Table 8.1.4.2.5 Abnormal and clinically significant changes in mean hematology values at 36 hours (or as indicated) **from** the RESTORE trial[a].

| Lab adverse event | Tirofiban (+Heparin) n=1070[b] | Placebo (+Heparin) n=1071[b] |
|---|---|---|
| **Hemoglobin (g/dl)** | | |
| 6 hours | -0.82 | **0.184** |
| 24 hours | -1.16 | **-0.98** |
| 36 hours | -1.16 | **-0.9** 1 |
| **Hematocrit (%)** | | |
| 6 hours | **-2.92** | -2.71 |
| 24 hours | -3.42 | -2.79 |
| 36 hours | -3.41 | -2.65 |
| **WBC count ($10^3/mm^3$)** | -1.38 | -0.50 |
| **Platelet count ($10^3/mm^3$)** | | |
| 6 hours | -5.62 | -12.14 |
| 24 hours | **-9.34** | -15.56 |
| 36 hours | -12.73 | -17.68 |
| **Eosinophils (%)** | 0.25 | 0.35 |

a. Data f n NDA volume 1.65, ref. 11, appe ix 4.1.1.
b. The actual number of subjects with available data is lower than the number of subjects entered into the trial.

8.1.4.2 Analyses Focused On Changes in Mean **Laboratory Measurements (cont)**

Table 8.1.4.2.6 Abnormal and clinically significant changes in mean lab values at 36 hours (or as indicated) from the RESTORE trial[a]

| Lab adverse event | **Tirofiban (+Heparin) n=1070** [b] | **Placebo (+Heparin) n=1071** [b] |
|---|---|---|
| Total **Bilirubin (mg/dl)** | -0.04 | -0.06 |
| **BUN (mg/dl)** | -0.30 | -0.83 |
| **Creatinine (mg/dl)** | 0.02 | 0.04 |
| **ALT (U/L)** | 4.19 | 5.03 |
| **Alkaline Phosphatase (U/l)** | -3.34 | -2.09 |

a. Data from NDA volume 1.65, ref. 11, appendix 4.1.1.
b. The actual number of subjects with available data is lower than the number of subjects entered into the trial.

8.1.4.3 Analyses Focused on **Outliers**

The first table shows the number and percentage of subjects with specific laboratoq values outside the normal range for lab test in 20.5% of tested subjects, where at least 300 subject have at least one measurement available. Shaded rows are for labs where the incidence varies ≥2X, or where there is ≥2% change in the incidence rate, between tirofiban and heparin groups. For a lab abnormality to be included in this table, it was first identified as an AE by the individual investigator. The data then was then reviewed by the sponsor, and the lab value had to fall outside the normal range.

Table 8.1.4.3.1 Incidence of labs outside the normal range in the phase II-II trials[a].

| | **Tirofiban + Heparin** | **Heparinl Procedures** | **Tirofiban** | **Heparinl No Procedures** | Total Heparin Alone |
|---|---|---|---|---|---|
| **Hematology** | 134/1944 (6.9%) | 132/1880 (7.0%) | 163/2002 (8.1%) | 94/1633 (5.8%) | 22613563 (6.4%) |
| aPTT increased | 7/1022 (0.7%) | 4/1014 (0.4%) | -o/o | o/o | 4/ 1014 (0.4%) |
| Eosinophils increased | 111793 (0.1%) | 2/1700 (0.1%) | 1111931 (0.6%) | 3/1558 (0.2%) | 5/3258 (0.2%) |
| Hematocrit decreased | 42/1938 (2.2%) | 49/1873 (2.6%) | 51/1996 (2.6%) | 27/1628 (1.7%) | 76/3501 (2.2%) |
| Hemoglobin decreased | 40/1938 (2.1%) | 5911875 (3.1%) | 57/1997 (2.9%) | 34/1631 (2.1%) | 93/3506 (2.6%) |
| Monocytes increased | 2/1793 (0.1%) | 111700 (0.1%) | 9/1931 (0.5%) | 3/1558 (0.2%) | 4/3258 (0.1%) |
| Platelet count decreased | 36/1934 (1.9%) | 34/1869 (1.8%) | 4411993 (2.2%) | 15/1625 (0.9%) | 49/3494 (1.4%) |
| Platelet count adverse events[b] | 51/1326 (2.6%) | 56/1869 (3.0%) | 56/1993 (2.8%) | 19/1583 (1.2%) | 75/3452 (2.2%) |
| **Serum Chemistry** | 210/1927 (10.9%) | 215/187(1 11.5%) | 115/2015 (5.7%) | 80/1640 (4.9%) | 295/3511 (8.4%) |
| ALT increased | 63/1709 (3.7%) | 64/1647 (3.9%) | 1711869 (0.9%) | 17/1529 (1.1%) | 81/3 176 (2.6%) |
| AST increased | 78/1811 (4.3%) | 66/1752 (3.8%) | 18/1864 (1.0%) | 18/1527 (1.2%) | 84/3279 (2.6%) |
| BUN increased | 9/1883 (0.5%) | 7/1817 (0.4%) | 9/1869 (0.5%) | 2/1532 (0.1%) | 9/3349 (0.3%) |
| CPK-MB increased | 7/1127 (0.6%) | 2/1143 (0.2%) | 0/1188 (0.0%) | 0/965 (0.0%) | 2/2108 (0.1%) |
| Serum albumin decreased | 12/1795 (0.7%) | 8/1738 (0.5%) | 4/1864 (0.2%) | 111526 (0.1%) | 9/3378 (0.3%) |
| Serum alkaline phosphatase up | 711792 (0.4%) | 4/1730 (0.2%) | 4/1866 (0.2%) | 2/1254 (0.1%) | 6/2984 (0.2%) |
| Serum calcium decreased | 13/1822 (0.7%) | 1511768 (0.8%) | 6/1867 (0.3%) | 6/1527 (0.4%) | 21/3295 (0.6%) |
| Serum CPK increased | 9/1812 (0.5%) | 9/1778 (0.5%) | 3/1927 (0.2%) | 011600 (0.0%) | 9/3378 (0.3%) |
| Serum creatinine increased | 10/1888 (0.5%) | 17/1824 (0.9%) | 1011868 (0.5%) | 7/1529 (0.5%) | 24/3353 (0.7%) |
| Serum glucose increased | 13/1864 (0.7%) | 18/1795 (1.0%) | 20/1865 (1.1%) | 18/1524 (1.2%) | 36/3369 (1.1%) |
| Serum magnesium decreased | 8/817 (1.0%) | 9/796 (1.1%) | 2/1859 (0.1%) | 111523 (0.1%) | 10/2319 (0.4%) |
| Serum phosphorus decreased | 9/1737 (0.5%) | 9/1697 (0.5%) | 1/1860 (0.1%) | 3/1521 (0.2%) | 12/32 18 (0.4%) |
| Serum potassium decreased | 52/1890 (2.8%) | 51/1828 (2.8%) | 22/1863 (1.2%) | 1111529 (0.7%) | 62/3357 (1.8%) |
| Serum total bilirubin increased | 2/1819 (0.1%) | 7/1749 (0.4%) | 1/1868 (0.1%) | 0/1530 (0%) | 7/3279 ((0.2%) |
| **Urinalysis** | 329/1701 (19.3%) | 268/1648 (16.3%) | 237/1911 (12.4%) | 130/1564 (8.3%) | 398/3212 (12.4%) |
| Urine bilirubin increased | 6/645 (0.9%) | 3/659 (0.5%) | 8/1656 (0.5%) | 1/1383 (0.1%) | 4/2042 (0.2%) |
| Urine blood increased | 161/1506 (10.7%) | 120/1538 (7.8%) | 181/1832 (9.9%); | 94/1518 (6.2%) | 214/3056 (7.0%) |
| Urine glucose increased | 14/1694 (0.8%) | 17/1636 (1.0%) | 20/1908 (1.0%) | 17/1557 (1.1%) | 34/3198 (1.1%) |
| Urine protein increased | 24/1692 (1.4%) | 20/1638 (1.2%) | 3311905 (1.7%) | 20/1558 (1.3%) | 40/3196 (1.2%) |
| **Miscellaneous** | 71/370 (19.2%) | 45/355 (12.7%) | 85/876 (9.7%) | 34/701 (4.9%) | 79/1056 (7.5%) |
| Fecal occult blood | 67/367 (18.3%) | 43/353 12.2%) | 85/871 (9.8%) | 34/696 (4.9%) | 77/1049 (7.3%) |

a. Data from NDA volume 1.2, Table C-39, volume 1.37, Table D-63, and electronic datasets.
b. Per protocol, platelet counts that decreased more than 1/3 from baseline were counted as an adverse event, whether or not the platelet count fell within the normal range. This row reflects the numbers of these events.

8.1.4.3 Analyses Focused on Outliers (cont)

The sponsor also defined a series of pm-defined critical limits, and collected data on the number of subjects with a value or a change in laboratory test outside of the limit. Some labs were not identified as potential AEs by this method:

1. ALT had no critical value, as its elevation could result from either hepatic or cardiac sources;
2. GGT had not critical value, as it was not routinely measured by the investigators (per protocol).

Also included in the table below are the number of subjects with available data. There was a higher incidence of hematocrit and hemoglobin decreases outside predefined limits in the tirofiban groups compared to the respective heparin groups, consistent with the higher incidence of mild bleeding observed with tirofiban, especially when used concomitantly with heparin. In general, there was a higher incidence of platelet count decreases with tirofiban compared to the heparin control groups.

Table 8.1.4.3.2 Number and percentage of subjects with a value or a change in lab value outside of defined limits in the phase II-III trials of ti fiban from NDP 0-912[a].

| | Tirofiban Heparin | Heparin/ Procedures | Tirofiban | Heparin/ No Procedures | Total Heparin Alone |
|---|---|---|---|---|---|
| **Hematology** | | | | | |
| Basophils: value 23 | 39/1063 (3.7%) | 21/1076 (2.0%) | 39/975 (4.0%) | 34/769 (4.4%) | 55/1845 (2.9%) |
| Eosinophils: value ≥5 | 150/1105 (13.6%) | 168 /1112 (15.1%) | 199/990 (20.1%) | 1524765 (19.9%) | 320/1877 (17.0%) |
| Hematocrit: decrease 210% | 193/1785 (10.8%) | 172/1811 (9.5%) | 94/1887 (5.0%) | 56/1551 (3.6%) | 228/3362 (6.8%) |
| Hemoglobin: decrease 23.5 g/dL | 174/1787 (9.7%) | 148/1815 (8.2%) | 71/1891 (3.8%) | 41/1561 (2.6%) | 189/2376 (8.0%) |
| Platelet count: decrease >1/3 | 101/1771 (5.7%) | 11 1/1800 (6.2%) | 94/1881 (5.0%) | 50/1549 (3.2%) | 16 113349 1'4.8%) |
| Platelet count: value <100,000/mm$^3$ | 35/1771 (2.0%) | 25/1800 (1.4%) | 29/1881 (1.5%) | 11/1549 (0.7%) | 36/3349 (1.1%) |
| WBC count: value <4500/mm$^3$ | 68/1729 (3.9%) | 65 1758 (3.7%) | 76/1887 (4.0%) | 83/1558 (5.3%) | 148/3316 (4.5%) |
| WBC count: value ≥14,000/mm | 53/1729 (3.1%) | 59/1758 (3.4%) | 1 11887 (0.1%) | 3/1558 (0.2%) | 62/3316 (1.9%) |
| **Blood Chemistry** | | | | | |
| Serum albumin: decrease >0.5 g/dL | 443/1478 (30.0%) | 446/1500 (29.7%) | 369/1636 (22.6%) | 246/1340 (18.4%) | 692/2840 (24.4%) |
| Serum albumin: increase >0.5 g/dL | 35 /1478 (2.4%) | 51/1500 (3.4%) | 63/1636 (3.9%) | 57/1340 (4.3%) | 108/2840 (3.8%) |
| Serum alkaline phosphatase: increase >30 U/dl | 45/1462 (3.1%) | 55/1492 (3.7%) | 30/1602 (1.9%) | 22/1329 (1.7%) | 77/2821 (2.7%) |
| ALT: increase >30 U/L | 180/1399 (12.9%) | 194/1432 (13.5%) | 65/1639 (4.0%) | 69/1342 (5.1%) | 263/2774 (9.5%) |
| Bilirubin: increase >0.4 mg/dL | 114/1518 (7.5%) | 96 /1537 (6.2%) | 139/1639 (8.5%) | 87/1343 (6.5%) | 183/2880 (6.4%) |
| BUN: increase >10 mg/dL | 59/1700 (3.5%) | 58/1707 (3.4%) | 71/1639 (4.3%) | 46/1344 (3.4%) | 104/3051 (3.4%) |
| Serum calcium: decrease >1.5 mg/dL | 43/1535 (2.8%) | 48/1557 (3.1%) | 32/1637 (2.0%) | 17/1340 (1.3%) | 6512897 (2.2%) |
| Serum calcium: increase >1.5 mg/dL | 17/1535 (1.1%) | 6/1557 (0.4%) | 14/1637 (0.9%) | 1111340 (0.8%) | 17/2897 (0.6%) |
| Serum chloride: decrease >10 mEq/L | 29/1649 (1.8%) | 25 /1664 (1.5%) | 31/1637 (1.9%) | 24/1339 (1.8%) | 49/2896 (1.7%) |
| Serum chloride: increase >10 mEq/L | 30/1649 (1.8%) | 23/1664 (1.4%) | 17/1637 (1.0%) | 24/1339 (1.8%) | 47/2896 (1.6%) |
| Serum creatinine: increase >0.4 mg/dL | 55/1714 (3.2%) | 7111721 (4.1%) | 80/1642 (4.9%) | 65/1342 (4.8%) | 136/3063 (4.4%) |
| Serum glucose: increase >60 mg/dL | 197/1655 (11.9%) | 198/1665 (11.9%) | 270/1628 (16.6%) | 207/1335 (15.5%) | 405/3000 (13.5%) |
| Serum phosphorus: decrease >1.0 mg/dL | 171/1414 (12.1%) | 187/1467 (12.7%) | 176/1594 (11.0%) | 12911320 (9.8%) | 316/2787 (11.3%) |
| Serum phosphorus: increase >1.O mg/dL | 244/1414 (17.3%) | 2650467 (18.1%) | 327/1594 (20.5%) | 264/1320 (20.0%) | 529/2787 (19.0%) |
| Serum potassium: decrease >1.0 mEq/L | 50/1673 (3.0%) | 58/1701 (3.4%) | 48/1595 (3.0%) | 37/1320 (2.8%) | 95/3021 (3.1%) |
| Serum potassium: increase >1.O mEq/L | 58/1673 (3.5%) | 57/1701 (3.4%) | 7511595 (4.7%) | 65/1320 (4.9%) | 122/3021 (4.0%) |
| Serum proteins: decrease >1.0 g/dl | 292/1490 (19.6%) | 281/1515 (18.5%) | 210/1636 (12.8%) | 142/1340 (10.6%) | 423/2855 (14.8%) |
| Serum proteins: increase >1.0 g/dL | 38/1490 (2.6%) | 56/1515 (3.7%) | 61/1636 (3.7%) | 54/1340 (4.0%) | 1 10/2855 (3.8%) |
| Serum sodium: decrease >10 mEq/L | 23/1701 (1.4%) | 24/1712 (1.4%) | 32/1637 (2.0%) | 25/1339 (1.9%) | 49/3051 (1.6%) |
| Serum sodium: increase >10 mEq/L | 18/1701 (1.1%) | 23/1712 (1.3%) | 23/1637 (1.4%) | 17/1339 (1.3%) | 40/3051 (1.3%) |
| Serum uric acid: increase >1.0 mg/dL | 149/1456 (10.2%) | 173/1478 (11.7%) | 229/1636 (14.0%) | 277/1340 (20.7%) | 450/2818 (16.0%) |
| **Urinalysis** | | | | | |
| Urine blood: increase ≥1 unit | 104/496 (21.0%) | 103/520 (19.8%) | 201/1143 (17.6%) | 112/949 (11.8%) | 215/1469 (14.6%) |
| Urine blood: vaiue off or worse | 136/444 (30.6%) | 129/450 (28.7%) | 261/1143 (22.8%) | 153/949 (16.1%) | 282/1399 (20.2%) |
| Urine blood: value of ++ or worse | 70/444 (5.8%) | 72/450 (16.0%) | 132/1143 (11.5%) | 801949 (8.4%) | 152/1399 (10.9%) |
| Urine blood: value of +++ or worse | 40/444 (9.0%) | 40/450 (8.9%) | 68/1 143 (5.9%) | 391949 (4.1%) | 7911399 (5.6%) |
| Urine glucose: increase 22 units | 7 /348 (2.0%) | 11/351 (3.1%) | 31/826 (3.8%) | 20/712 (2.8%) | 3 1/1063 (2.9%) |
| Urine protein: increase >I unit | 29/340 (8.5%) | 29/347 (8.4%) | 57/800 (7.1%) | 50/684 (7.3%) | 79/103117.7 |

a. Data from NDA volume 1.3 Table D-70 and ele onic datasets.

**8.1.4.3 Analyses Focused on Outliers**

Finally, data on subjects who had an SAE related to a laboratory value were also collected. The first table summarizes these subjects. The number of lab-related SAEs was quite small in the database.

Table 8.1.4.3.3 Number and percentage of subjects with laboratory SAEs (20.5% in any treatment group) from NDA 20-9 12".

| | Tirofiban + Heparin | Heparin/ Procedures | Tirofiban | Heparin/ No Procedures | Total Heparin Alone |
|---|---|---|---|---|---|
| Hematology | 5/1944 (0.3%) | 3/1880 (0.2%) | 4/2002 (0.2%) | 2/1633 (0.1%) | 5/3513 (0.1%) |
| Serum Chemistry | 0/1927 (0%) | 3/1871 (0.2%) | 4/2002 (0.2%) | 2/1633 (0.1%) | 5/3504 (0.1%) |
| Urinalysis | 0/1071 (0%) | 1/1648 (0.1%) | 1/1911 (0.1%) | 0/1564 (0%) | 1/3212 (0.1%) |

a. Data from NDA volume 1.37, Table D-66 and electronic datasets.

A listing of the SAEs associated with lab abnormalities is found in appendix 3, section 15. I. Fifteen of the 23 SAEs related to lab abnormalities were bleeding-related, with 6 in the tirofiban group, 2 in the tirofiban +heparin, and 7 in the heparin alone group.

**8.1.4.4 Vital Signs**

No data were collected on the effect of tirofiban on heart rate, respiratory rate, or blood pressure. The data on the incidence of abnormal heart rates are included in the ECG/ special examinations data below. Changes in blood pressure (i.e., hypotension, hypertension) and pulse rate (i.e., bradycardia, tachycardia, asystole) were included in both the AEs and the SAEs collected in all trials. The rates of occurrence for SAEs in these relevant categories were all low, but are included in the table below.

Table x.1.4.4.1 Number and percentage of subjects with SAEs related to vita1 signs in the phase II-III database".

| | Tirofiban | Tirofiban + Heparin | Total Heparin Alone |
|---|---|---|---|
| Syncope | 2 (0.1%) | 1 (0.1%) | 3 (0.1%) |
| Asystole | 3 (0.1%) | 8 (0.4%) | 9 (0.3%) |
| Atrial tachycardia | 0 (0%) | 0 (0%) | 1 (0.1%) |
| Blood pressure decreased | 3 (0.1%) | 2 (0.1%) | 4 (0.1%) |
| Bradycardia | 3 (0.1%) | 2 (0.1%) | 4 (0.1%) |
| Hypertension | 1 (0.1%) | 2 (0.1%) | 0 (0%) |
| Hypertensive crisis | 1 (0.1%) | 0 (0%) | 1 (1%) |
| Hypotension | 15 (0.7%) | 9 (0.5%) | 19 (0.5%) |
| Sinus tachycardia | 28 (1.4%) | 20 (1.0%) | 34 (1.0%) |
| Tachycardia | 0 (0%) | 0 (0%) | 2 (0.1%) |
| Tachycardia-Bradycardia Syndrome | 1 (0.1%) | 0 (0%) | 1 (0.1%) |

a Data from NDA volume 1.65, ref 88.

8.1.4.5 **ECGs** and Special Examinations

No specific data on the effect of tirofiban on the incidence of ECG abnormalities were collected. The table below summarizes the incidence of adverse events within the cardiovascular system identified by individual investigators through examinations, including ECGs. Note that in the tirofiban alone group there was an increased incidence of atria1 fibrillation, bradycardia, PVCs, sinus bradycardia and ventricular tachycardia, relative to the heparin/ no procedures group.

Table 8.1.4.5.1 Cardiovascular AEs detected as a result of special exams, including ECGs, from the phase II-III safety database with an incidence of >0.5% in any treatment group[a].

| Lab adverse event | Tirofiban + Heparin n=1953 | Heparin/ Procedures n=1887 | Tirofiban n=2032 | Heparin/ No Procedures n=1659 | Total Heparin Alone n=3546 |
|---|---|---|---|---|---|
| **Cardiovascular system** | 104 (5.3%) | 141 (7.5%) | 104 (5.1%) | 31 (1.9%) | 172 (4.8%) |
| Atrial fibrillation | 4 (0.2%) | 10 (0.5%) | 8 (0.4%) | 1 (0.1%) | 11 (0.3%) |
| Bradycardia | 7 (0.4%) | 14 (0.7%) | 14 (0.7%) | 3 (0.2%) | 17 (0.48%) |
| PVCs | 27 (1.4%) | 43 (2.3%) | 28 (1.4%) | 6 (0.4%) | 49 (1.4%) |
| Sinus arrhythmia | 9 (0.5%) | 7 (0.4%) | 4 (0.2%) | 0 (0%) | 7 (<0.1%) |
| Sinus bradycardia | 18 (0.9%) | 21 (1.1%) | 16 (0.8%) | 1 (0.1%) | 22 (0.6%) |
| Ventricular tachycardia | 11 (0.6%) | 14 (0.7%) | 13 (0.6%) | 1 (0.1%) | 15 (0.4%) |

a. Data from NDA volume 1.37, table D-67. Subjects with more than one abnormality from special examinations were counted only once in the body system total and the overall total.

Abnormalities which would have been detected by ECGs were also captured in the SAE events table, and are summarized below. The incidence of almost all of these SAEs was <1%.

Table 8.1.4.5.2 Number and percentage of subjects with SAEs related to vital signs in the phase II-III database'.

| | Tirofiban | Tirofiban+ Heparin | Total Heparin Alone |
|---|---|---|---|
| **Atrial tachycardia** | **0 (0%)** | **0 (0%)** | **1** (0.1%) |
| **Sinus tachycardia** | 28 (1.4%) | 20 (1.0%) | **34** (1.0%) |
| **Arrhythmia** | **1 (0.1%)** | 1 **(0.1%)** | 4 (0.1%) |
| **AV Block, second degree** | **1** (0.1%) | **0 (0%)** | 2 (0.1%) |
| **AV Block, third degree** | 2 (0.1%) | **1 (0.1%)** | 3 (0.1%) |
| **AV Conduction Disorder** | 0 (0%) | **0 (0%)** | 2 (0.1%) |
| **Bigeminy/ Trigeminy/ Quadrageminy** | 0 (0%) | **0 (0%)** | **1** (0.1%) |
| **ECG Abnormality** | 0 (0%) | **0 (0%)** | 1 (0.1%) |
| **Electromechanical Dissociation** | 4 (0.2%) | 1 (0.1%) | 3 (0.1%) |
| **PVCs** | 0 (0%) | 0 (0%) | 1 (0.1%) |
| **Supraventricular tachycardia** | 0 (0%) | 2 (0.1%) | 0 (0%) |
| **Ventricular Arrhythmia** | 0 (0%) | **1** (0.1%) | 1 (0.1%) |
| **Ventricular Fibrillation** | **10 (0.5%)** | 12 (0.6%) | 20 (0.6%) |
| **Ventricular Tachycardia** | (70.3%) | (60.4%) | 10 (0.3%) |

a Data from NDA volume 1.65, ref 88.

## 8.1.5 Discontinuations

The next table shows a summary of the disposition of subjects in the phase II-III trials of tirofiban, including the dropouts. Compared with the total heparin group, the tirofiban +heparin group had a higher rate of overall discontinuation. This was due to a combination of fewer discontinuations for presumed clinical endpoints (4.97% vs. 6.6%) counterbalanced by a higher % discontinuation for non-bleeding clinical AEs (2.66% vs. 1.41%) and for both lab and clinical bleeding AEs (3.5% vs. 0.93%). The tirofiban groups both also had higher rates of discontinuation due to non-bleeding lab AEs than did the heparin-alone group.

Table 8.1.5.1 Disposition of subjects randomized in the phase II-III studies'.

| Patient Disposition | Tirofiban alone[b] | Tirofiban + Heparin | Heparin alone | Total |
|---|---|---|---|---|
| Randomized | 2032 | 1953 | 3546 | 753 l |
| Completed | 1796 (88%) | 1638 (83.8%) | 3060 (86.3%) | 6494 (86.2%) |
| Discontinued (Total) | 236 (11.6%) | 315 (16.1%) | 486 (13.7%) | 1037 (13.8%) |
| Presumed clinical endpoint[e] | 67 (3.3%) | 97 (4.97%) | 234 (6.6%) | 398 (5.28%) |
| Non-bleeding clinical AE[c] | 24 (1.2%) | 52 (2.66%) | 50 (1.41%) | 126 (1.67%) |
| Non-bleeding laboratory AE[c] | 8 (0.39%) | 12 (0.61%) | 4 (0.11%) | 24 (0.32%) |
| Bleeding lab or clinical AE[d] | 24 (1.2%) | 68 (3.5%) | 33 (0.93%) | 125 (1.6%) |
| Patient noncompliance | 5 (0.2%) | 4 (0.2%) | 6 (0.16%) | 15 (0.2%) |
| Protocol deviation | 49 (2.4%) | 26 (1.3%) | 71 (2.0%) | 146 (1.93%) |
| Patient withdrawn | | 11 (0.56%) | 25 (0.7%) | 57 (0.77%) |
| Did not receive drug | 30 21 (1.0%) (1.4%) | 7 (0.36%) | 33 (0.93%) | 70 ((0.92%) |
| Other reasons | 8 (0.39%) | 39 (2.00%) | 30 (0.85%) | 77 (1.02%) |

a. Data from individual study summaries, tables 6.2.1.12.2, 6.2.3.12.2.1, 6.2.2.12.2.1, 6.1.1.12.2.1, 6.1.2.12.2.1, and 6.1.3.12.2.1.

b. Based on a recommendation by the Data Safety Monitoring Board overseeing the trial, this arm was dropped after 345 subjects were entered.

c. Includes counts of subjects who discontinued due to nonbleedmg clinical or nonbleedmg laboratory adverse events, in their respective categories.

d. Includes clinical or laboratory adverse experiences.

e. Includes those subjects in the RESTORE trial who underwent stent placemtent (T+H=60, H+76).

### 8.1.5.2 Discontinuations associated with Serious Adverse Events (SAEs)

The next table summarizes the subjects who were withdrawn from study drug prematurely due to one or more serious adverse events. A listing of the individual subjects who were discontinued for serious adverse events can be found in appendix 3, section 15.0. Individual summaries for subjects discontinued for laboratory abnormalities ate found in appendix 5, section 17.0. This table should be compared with the two tables following, which summarize the subjects who were withdrawn with any adverse event, either bleeding or nonbleedmg.

As before, shading indicates AEs with ≥2X or ≥2% difference between respective tirofiban and heparin groups.

Table 8.1.5.2-l Serious adverse events leading to subject discontinuation, collected in the phase II-III tirofiban safety database*.

| Body System/ SAE | Tirofiban + Heparin n=1953 | Tirofiban n=2032 | Heparin n=3546 |
|---|---|---|---|
| Total # with SAEs leading to discontinuation | 33 (1.7%) | 20 (1.0%) | 32 (0.9%) |
| Body as a whole | 1 (0.1%) | 4 (0.2%) | 4 (0.1%) |
| Cardiovascular System | 20 (1.0%) | 6 (0.3%) | 21 (0.6%) |
| Digestive System | 6 (0.3%) | 6 (0.3%) | 1 (<0.1%) |
| Hemic & Lymphatic System | 1 (<0.1%) | 3 (0.1%) | 1 (<0.1%) |
| Metabolic/ Nutritional System | 0 (0%) | 0 (0%) | 1 (<0.1%) |
| Nervous System | 1 (<0.1%) | 0 (0%) | 3 (<0.1%) |
| Respiratory System | 0 (0%) | 0 (0%) | 3 (<0.1%) |
| Dermatologic System | 1 (<0.1%) | 0 (0%) | 0 (0%) |
| Special Senses System | 0 (0%) | 0 (0%) | 1 (<0.1%) |
| Urogenital System | 5 (0.3%) | 1 (<0.1%) | 1 (<0.1%) |

a. Data from NDA volume 1.37, Table D-62 and electronic datasets.

b. Individual summaries for subjects discontinued far laboratory abnormalities are found in appendix 4, section 17.0.

8.1.5.3 Discontinuations associated **with Adverse Events (AEs)**

**The next** table summarizes the subjects who were withdrawn from study drug prematurely due to one or more non-serious adverse events. A listing of the individual subjects who were discontinued for adverse events can be found in appendix 4, section 16.0. The data are divided into subjects who were withdrawn for either bleeding or nonbleeding AEs. As before, shading indicates AEs with ≥2X or ≥2% difference between respective tirofiban and heparin groups.

Table 8.1.5.3.1 Nonbleeding adverse events leading to subject discontinuation, collected in the phase II-III ıfetydatabase".

| Body System/ SAE | Tirofiban + Heparin n=1953 | Heparinl Procedures n=1887 | Tirofiban n=2032 | Heparinl No Procedures n=1659 | Total Heparin Alone n=3546 |
|---|---|---|---|---|---|
| **Total # with nonbleeding AEs leading to discontinuation** | **39 (2.0%)** | **34 (1.8%)** | **22 (1.1%)** | **15 (0.9%)** | **49 (1.4%)** |
| **Body as a whole** | 3 (0.2%) | 4 (0.2%) | 5 (0.2%) | 2 (<0.1%) | 6 (0.1%) |
| **Cardiovascular System** | 22 (1.1%) | 17 (0.9%) | 7 (0.3%) | 5 (0.3%) | 22 (0.6%) |
| **Digestive System** | 1 (<0.1%) | 0 (0%) | 3 (0.1%) | 2 (<0.1%) | 2 (<0.1%) |
| **Hemic & Lymphatic System** | 5 (0.3%) | 1 (<0.1%) | 5 (0.2%) | 1 (<0.1%) | 2 (<0.1%) |
| **Metabolic/ Nutritional System** | 0 (0%) | 1 (<0.1%) | 1 (<0.1%) | 0 (0%) | 1 (<0.1%) |
| **Nervous System** | 5 (0.3%) | 7 (0.4%) | 1 (<0.1%) | 4 (0.2%) | 11 (0.3%) |
| **Respiratory System** | 0 (0%) | 3 (0.2%) | 0 (0%) | 1 (<0.1%) | 4 (0.1%) |
| **Dermatologic System** | 3 (0.2%) | 3 (0.2%) | 0 (0%) | 0 (0%) | 3 (<0.1%) |
| **Special Senses System** | 0 (0%) | 0 (0%) | 0 (0%) | 1 (<0.1%) | 1 (<0.1%) |
| **Urogenital System** | 3 (0.2%) | 1 (<0.1%) | 0 (0%) | 0 (0%) | 1 (<0.1%) |

a. Data from NDA volume 1.37, Table D-46 and electronic datasets.

Table 8.1.5.3.2 Bleeding adverse events leading to subject discontinuation, collected in the phase II-III safety database'.

| Body System/ SAE | Tirofiban + Heparin n=1953 | Heparin/ Procedures n=1887 | Tirofiban n=2032 | Heparin/ No Procedures n=1659 | Total Heparin Alone n=3546 |
|---|---|---|---|---|---|
| **Total # with bleeding AEs leading to discontinuation** | **71 (3.6%)** | **19 (1.0%)** | **22 (1.1%)** | **6 (0.4%)** | **25 (0.7%)** |
| **Cardiovascular System** | 41 (2.1%) | 13 (0.7%) | 3 (0.1%) | 1 (0.1%) | 14 (0.4%) |
| Bleeding, postoperative | 24 (1.2%) | 5 (0.3%) | 1 (<0.1%) | 0 (0%) | 5 (0.1%) |
| Hematoma | 15 (0.8%) | 5 (0.3%) | 0 (0%) | 0 (0%) | 5 (0.1%) |
| **Digestive System** | 19 (1.0%) | 4 (0.2%) | 11 (0.5%) | 1 (0.1%) | 5 (0.1%) |
| **Hemic & Lymphatic System** | See labs | | | | |
| **Respiratory System** | 5 (0.3%) | 0 (0%) | 4 (0.2%) | 1 (0.1%) | 1 (<0.1%) |
| **Dermatologic System** | 2 (<0.1%) | 0 (0 %) | 0 (0%) | 0 (0 %) | 0 (0%) |
| **Urogenital System** | 11 (0.6%) | 3 (0.2%) | 4 (0.2%) | 3 (0.2%) | 6 (0.4%) |

a. Data from NDA volume 1.37, Table D-49 and electronic datasets.

**8.1.5.4 Discontinuations associated with Laboratory Adverse Events**

The dropouts for laboratory abnormalities are listed in appendix 5, section 17.0. As shown the first table below, hematologic abnormalities were the most common causes of discontinuation due to lab abnormalities, accounting for all but one subject discontinuation.

Table 8.1.5.4.1 Laboratory adverse events leading to subject discontinuation, collected in the phase II-III safety database".

| | Tirofiban n=2032 | Tirofiban + Heparin n=1953 | Heparin n=3546 |
|---|---|---|---|
| **All lab AEs** | 10 (0.5% | 16 (0.8%) | 12 (0.3%) |
| **Hematologic AEs[b]** | 10 (0.5%) | 16 (0.7%) | 11 (0.3%) |
| **Non-hematologic AEs[c]** | 0 (0%) | 0 (0%) | 1 (<0.1%) |

a. Data from appendix 17.

b. Included alterations in platelet count, hemoglobin/hematocrit, prothrombin time and activated partial thromboplastin time, or associated with bleeding.

c. Includes a single subject discontinued for elevated serum creatinine.

## 15.0.2 Subjects in Tirofiban + Heparin group with serious adverse events (SAEs)

Table 15.0.2.1 SAEs in the tirofiban +heparin group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| TIROFIBAN + HEPARIN | | | | | |
| *RESTORE TRIAL* | | | | | |
| 013-002 2363 | 51 M | 1 | Pain, chest | None | Recovered |
| 013-002 2368 | 53 M | 2 | Ischemia, myocardial | None | Continuing |
| 013-003 1286 | 67 M | 2<br>9 | CVA, hemorrhagic<br>Death | D/C'd | Death |
| 313-003 2236 | 75 M | 2 | Hemorrhage, gastrointestinal | None | Recovered |
| 013-003 2947 | 79 M | 2<br>2<br>2<br>3<br>3 | Chills<br>Fever<br>Tremor<br>Chills<br>Tremor | D/C'd | Recovered |
| 013-003 2952 | 68 M | 1<br>1 | Hallucinations<br>Confusion | None | Recovered |
| 013-003 2954 | 57 F | 2 | Infection, urinary tract | None | Recovered |
| 013-003 2954 | 57 F | 3 | Infection, pelvic | None | Recovered |
| 013-003 3136 | 52 M | 6 | Pain, chest | None | Recovered |
| 013-003 3141 | 77 F | 6<br>6<br>11 | Septicemia<br>Infection, urinary tract<br>Endocarditis | None | Recovered |
| 013-003 3144 | 75 M | 2<br>4<br>4<br>5<br>5<br>6<br>10<br>28<br>29 | Aneurysm, heart<br>Respiratory failure<br>Hemorrhage, gastrointestinal<br>Renal insuffkiency<br>Thrombosis, vein<br>Effusion, pleural<br>Edema, pulmonary<br>Aneurysm, heart<br>Death | None | Death |
| 013-004 1235 | 54 M | 1 | Drug overdose | None | Recovered |
| 013-004 3749 | 52 F | 10 | Pain, chest | None | Recovered |
| 013-006 1061 | 74 M | 2 | Bacteremia | None | Recovered |
| 013-006 1675 | 43 M | 12 | Cellulitis | None | Recovered |
| 013-007 1302 | 54 M | 16 | Angina pectoris | None | Recovered |
| 013-007 1305 | 52 M | 9<br>11<br>12 | Angina, unstable<br>Myocardial infarction<br>Dissection, coronary artery | None | Recovered |
| 013-007 1309 | 61 M | 12 | Pain, chest | None | Recovered |
| 013-008 1723 | 64 M | | Drug overdose | None | Recovered |
| 013-008 1725 | 67 M | 1<br>16 | Dissection, coronary artery<br>Effusion, pericardial | None | Continuing |
| 013-008 1731 | 50 M | 3 | Thrombus, ventricular | None | Continuing |
| 013-009 2568 | 73 F | 6 | Pain, chest | None | Recovered |
| 013-009 2570 | 63 M | | Angina pectoris | None | Recovered |
| 013-009 2572 | 41 M | 3 | Pain, chest | None | Recovered |
| 013-009 3214 | 46 M | 28 | Dissection, coronary artery | D/C'd | Resolved |
| 013-011 1528 | 40 M | 1<br>8 | Dissection, coronary artery<br>Pseudoaneurysm | D/C'd | Resolved |
| 013-011 2354 | 44 M | 31 | Myocardial infarction | None | Recovered |
| 013-013 2227 | 56 M | 29 | Pain, chest | None | Recovered |
| 013-013 2624 | 73 F | 8 | Bleeding, postoperative | None | Recovered |

8.1.5.4 Discontinuations associated **with Laboratory** Adverse Events **(cont)**

Of the hematologic AEs leading to discontinuation, the majority were discontinuations for decreased platelet count/ thrombocytopenia or for decreased hemoglobin. The table below summarizes the incidence of discontinuation for these two abnormalities. A higher percentage of subjects in of the tirofiban groups were discontinued for decreased platelet counts compared with subjects in the heparin alone group. A higher percentage of subjects in the heparin group were discontinued for decreased hemoglobin concentrations.

Table 8.1.5.4.2 Dropouts for hematologic lab abnormalities from the phase II-III safety database with an incidence of >0.1% in any treatment group.

| Lab adverse event | Tirofiban n=1953 | Tirofiban + Heparin n=2052 | Heparin n=3546 |
|---|---|---|---|
| Thrombocytopenia or 'Platelet count decreased' | 8 (0.4%) | 10 (0.5%) | 2 (<0.1%) |
| Decreased hemoglobin | 2 (0.1%) | 1 (<0.1%) | 7 (0.2%) |

8.1.6 Special Studies

In this section, problems germane to all NDA submissions are reviewed: These include: tolerance; withdrawal/ rebound; abuse potential; human reproductive toxicity; and overdose.

8.1.6.1 Special Studies: Tolerance

In the Phase I randomized, double-blind, aspirin interaction crossover study (Protocol 002), each of 12 subjects received the following treatments on three separate occasions separated by a 14-day washout period: tirofiban alone, tirofiban and aspirin pretreatment, and aspirin pretreatment. The tirofiban infusion was at 0.15 µg/kg/min over 4 hours. Though presence of the use of aspirin is a potentially confounding factor in determining the possibility of development of resistance or tachyphylaxis in the subjects who received tirofiban twice, as expected, bleeding time extension with tirofiban was greater with aspirin pretreatment (4.1-fold versus 2.3-fold baseline). The additional effect on bleeding time with aspirin is unlikely related to tirofiban since the effect was similar to the estimated additional effect of aspirin pretreatment on an infusion of placebo in the study. Levels of inhibition of ADP-induced platelet aggregation with tirofiban were unaffected by the addition of aspirin suggesting that resistance or tachyphylaxis might be unlikely. None of the subjects exhibited any signs of anaphylaxis upon re-exposure to the tirofiban.

Per the sponsor, there were no subjects in Phase II or Phase III who received tirofiban twice.

8.1.6.2 Special Studies: Withdrawal/ Rebound

No specific testing for a 'rebound' effect following tirofiban withdrawal was conducted. Such a rebound might be expected to manifest as an increase in coagulability. In protocol 008, the percent inhibition of platelet aggregation (IPA) was measured at baseline, during tirofiban infusion, and for up to 8 hours post-infusion. As shown in the table below, the IPA declined rapidly after stopping tirofiban infusion, with no evidence for a rebound (compare tirofiban arms with placebo +heparin).

Table 8.1.6.2.1 (reproduces table 6.1.2.2.2d.5) Median IPA (%, values from protocol #007[a].

| Time of infusion | Tirofiban 5/0.5 +Heparin | Tirofiban 10/0.1 +Heparin | Tirofiban 10/0.15 +Heparin | Pooled Heparin |
|---|---|---|---|---|
| Bolus (5 mins) | 72.5* (57.5, 79.5) | 92.9* (87.6, 95.5) | 95.5* (83.9, 96.9) | -2.0 (-7.3, 5.1) |
| 2 hours | 47.1' (40.5, 70.1) | 94.3* (83.6, 96.3) | 100.0* (95.6, 100.0) | -3.4 (-13.1, 10.3) |
| End infusion | 57.1* (46.5, 72.6) | 90.9* (79.4, 94.6) | 94.6* (87.4, 97.3) | 2.5 (-10.6, 16.8) |
| 0.5 hrs post-infusion | 47.4* (34.3, 58.8) | 79.9* (66.0, 86.7) | 92.8* (76.7, 96.4) | 5.1 (-7.2, 11.8) |
| 1.5 hrs post-infusion | 28.6* (15.9, 46.2) | 50.4* (44.2, 64.8) | 79.0* (56.1, 86.8) | 3.7 (-8.3, 9.0) |
| 4 hrs post-infusion | 15.7 (7.5, 31.3) | 26.9" (15.6, 41.6) | 46.8* (24.1, 58.0) | -5.9 (-11.9, 3.7) |
| 8 hrs post-infusion | 12.0 (1.8, 16.7) | 2.3 (-3.0, 19.4) | 13.5 (2.4, 19.4) | -7.6 (-22.1, 3.3) |

a. Data from NDA volume 1.46, ref. 4, table 21.

b. * values differ from pooled heparin value <0.05. There was no significant difference between the three tirofiban groups

8.1.6.2 Special Studies: Withdrawal/ Rebound **(cont)**

Similarly, aPTT was monitored during and after the tirofiban (+heparin) infusion in the same trial. The results for the aPTT at the end of study drug infusion, and 10 hours later, are shown below. Note that the dose used in the phase III trials is closest to the tirofiban 10/0.15 dose.

Table 8.1.6.2.2 Median aPTT values (secs) from protocol #007[a].

| Time **of infusion** | **Tirofiban 5/0.5 +Heparin** | **Tirofiban 10/0.1 +Heparin** | **Tirofiban 10/0.15 +Heparin** | Pooled **Heparin** |
|---|---|---|---|---|
| **Pre-infusion** (off heparin) | **46.9** | **38.5** | **33.8** | **32.0** |
| End infusion | 59.3 | 69.9 | 42.9 | **53.0** |
| 10 hrs post-infusion | **25.6** | **33.5** | **35.1** | **31.9** |

a Data from NDA volume 1.46, ref. 4, table 236.

8.1.6.3 Special Studies: Abuse Potential

The anticipated abuse potential for tirofiban is quite low. First, it is administered intravenously. Second, it has no known mood-altering properties, and none are expected given it's proposed mechanism of action.

8.1.6.4 Special Studies: Human Reproduction Data

Per the sponsor, no pregnant individuals are known to have been exposed to tirofiban during the product development.

8.1.6.5 Special Studies: Overdose Experience

The first table below summarizes the number of subjects who received a tirofiban 'overdose,' in the phase II-III database.

Table 8.1.6.5.1 Subjects with tirofiban overdose in the phase II-III database'.

| Lab adverse event | Tirofiban **n=2032** | **Tirofiban + Heparin n=1953** |
|---|---|---|
| **Drug Overdose** | **36 (1.8%)** | **30 (1.5%)** |

a Data from NDA volume 1.37, table D-120.

Twelve subjects had overdoses of other medications, primarily heparin (8/12 non-tirofiban ODs, 75%).

Based on the specifics of the protocols in the phase II-III trials, a subject could have an overdose of tirofiban in three ways: 1) an inappropriately large dose of tirofiban bolus, 2) an inappropriately high dose of a loading infusion of tirofiban, or 3) an inappropriately high dose of a maintenance infusion (due either to an inappropriate duration of the loading infusion or to inappropriate calculation of the maintenance dose).

Since the major safety concern for tirofiban overdose is the inhibition of platelets, and the potential for increased bleeding; the table below summarizes the bleeding complications for these 66 subjects. The incidence of any bleeding complication was 56% (37/66 subjects) in the subjects who experienced an overdose of tirofiban (14/36 (38.9%) for the monotherapy subjects and 23/30 (76.7%) for the subjects who received tirofiban plus heparin). In these 37 subjects, most of the bleeding complications were minor, Of the 36 subjects with available data with a bleeding complication, 31/36, or 86.1%, had bleeding episodes that were classified by the investigator as oozing or mild in severity. Of the remaining 5 subjects, 4 subjects (2 in the tirofiban monotherapy overdose group and 2 in the tirofiban plus heparin overdose group) had a bleeding event classified as moderate in severity, defined as an observed blood loss of 250 to 500 ml (4/36 or 11.1%). The remaining patient (Protocol 006: AN 6141) had the only life-threatening bleed in the overdose cohort, which occurred more than 10 days after discontinuation of tirofiban monotherapy in the context 'of a surgical procedure.

8.1.6.5 Special Studies: Overdose Experience **(cont)**

The most common bleeding event was a bleed at the site of cardiac catheterization (15/66 patients, or 22.7% incidence in the overdose cohort). The incidence, but not the severity, of bleeding events was somewhat increased in the overdose patients who received tirofiban or tirofiban plus heparin, as compared to those observed in the overall cohort of acute coronary ischemic syndrome patients who received tirofiban or tirofiban plus heparin at doses defined in the individual protocols, This was especially true for epistaxis, IV site bleeding, and GI bleeding.

Table 8.1.6.5.2 Subjects with tirofiban overdose (OD) in the phase II-III database[a].

| 4ny Bleeding Complication | Tirofiban alone | | Tirofiban +Heparin | |
|---|---|---|---|---|
| | With OD (n=36) | Overall Cohort[b] (n=2032) | With OD (n=30)[c] | Overall Cohort[b] (n=1953) |
| **Patients with at least one bleeding complication** | 14 (38.9) | 638 (31.4) | 23 (76.7) | 1085 (55.6) |
| **Patients without bleeding complication** | 22 (61.1) | 1394 (68.6) | 7 (23.3) | 868 (44.4) |
| **Site of Bleeding** | | | | |
| **Catheter Site** | | | | |
| None | 32 (88.9) | 1877 (92.4) | 19 (63.3) | 1292 (66.2) |
| Any | 4 **(11.1)** | **155 (7.6)** | 11 (36.7) | 661 (33.8) |
| Oozing | 2 (5.6) | 72 (3.5) | 7 (23.3) | 468 (23.9) |
| **Mild** | **1 (2.8)** | 52 (2.6) | 4 (13.3) | 126 (6.4) |
| Moderate | 1 (2.8) | 23 (1.1) | 0 (0.0) | 56 (2.9) |
| Severe | 0 (0.0) | 6 (0.3) | 0 (0.0) | 10 (0.5) |
| Life Threatening | 0 (0.0) | 2 (0.1) | 0 (0.0) | 1 (0.1) |
| GI | | | | |
| None | 33 (91.7) | 1910 (94.0) | 26 (86.7) | 1829 (93.7) |
| Any | 3 (8.3) | 122 (6.0) | 4 (13.3) | 124 (6.3) |
| Oozing | 1 (2.8) | 57 (2.8) | 1 (3.3) | 43 (2.2) |
| Mild | 2 (5.6) | 43 (2.1) | 3 (10.0) | 53 (2.7) |
| Moderate | 0 (0.0) | 12 (0.6) | 0 (0.0) | 19 (0.9) |
| Severe | 0 (0.0) | 5 (0.2) | 0 (0.0) | 5 (0.3) |
| Life Threatening | 0 (0.0) | 5 (0.2) | 0 (0.0) | 4 (0.2) |
| **GU/Hematuria** | | | | |
| N&e | 33 (91.7) | 1818 (89.5) | 24 (80.0) | 1675 (85.8) |
| Any | 3 (8.3) | 214 (10.5) | 6 (20.0) | 278 (14.2) |
| Oozing | 0 (0.0) | 108 (5.3) | 1 (3.3) | 71 (3.6) |
| Mild | 3 (8.3) | 95 (4.7) | 4 (13.3) | 162 (8.3) |
| Moderate | 0 (0.0) | 10 (0.5) | 1 (3.3) | 40 (2.0) |
| Severe | 0 (0.0) | 1 (0.1) | 0 (0.0) | 3 (0.2) |
| Life Threatening | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Intracranial** | | | | |
| None | 36 (100) | 203 1 (99.9) | 30 **(100)** | 1952 (99.9) |
| Any | 0 (0.0) | 2 (0.1) | 0 (0.0) | 1 (0.1) |
| Oozing | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| Mild | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| Moderate | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Life Threatening | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) |

a. Data from NDA 20-913, volume 7.2, ref. 35, page 841. This table contains counts of patients. Patients with more man one bleeding complication in any one site are counted only once in that site.

b. Includes both non-overdose and overdose patients.

c. For one episode of bleeding, bleeding severity was not recorded.

d. In 6 patients in the overall tirofiban-alone cohort, a severity grade was not recorded. In 9 patients in the overall tirofiban + heparin cohort, a severity grade was not recorded.

e. 'Site Unknown' represents decreases in hematologic parameters considered clinically significant by the investigator, but that were not associated with overt bleeding. These events were reportable as bleeding complications, per data handling guidelines.

f. The site designation "hematoma" was restricted to the RESTORE trial and was largely localized to catheterization site bleeding.

Table 8.1.6.5.2 Subjects with tirofiban overdose (OD) in the phase II-III database (cont)[a].

| Any Bleeding Complication | Tirofiban alone | | Tirofiban +Heparin | |
|---|---|---|---|---|
| | With OD (n=36) | Overall Cohort[b] (n=2032) | With OD (n=30)[c] | Overall Cohort[b] (n=1953) |
| IV | | | | |
| None | 31 (86.1) | **1922 (94.6)** | 26 (86.7) | 1836 (94.0) |
| Any | 5 (13.9) | 110 (5.4) | 4 (13.3) | 117 (6.0) |
| Oozing | 4 (11.1) | 67 (3.4) | 4 (13.3) | 67 (3.4) |
| Mild | 1 (2.8) | 40 (1.9) | 0 (0.0) | 42 (2.2) |
| **Moderate** | 0 (0.0) | 3 (0.1) | 0 (0.0) | 8 (0.4) |
| **Severe** | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Life Threatening | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Oral/Mouth** | | | | |
| **None** | 36 (100) | 2012 (99.0) | 29 (96.7) | 1902 (97.4) |
| Any | 0 (0.0) | 20 (1.0) | 1 (3.3) | 51 (2.6) |
| Oozing | 0 (0.0) | 12 (0.6) | 0 (0.0) | 18 (0.9) |
| Mild | 0 (0.0) | 7 (0.3) | **1 (3.3)** | 31 (1.6) |
| Moderate | 0 (0.0) | 1 (0.1) | **0 (0.0)** | 2 (0.1) |
| Severe | 0 (0.0) | 0 (0.0) | **0 (0.0)** | 0 (0.0) |
| Life Threatening | 0 (0.0) | 0 (0.0) | **0 (0.0)** | 0 (0.0) |
| **Epistaxis (Nosebleed)** | | | | |
| **None** | 33 (91.7) | 1905 (93.7) | 27 (90.0) | 1846 (94.5) |
| Any | 3 (8.3) | 127 (6.3) | 3 (10.0) | 107 (5.5) |
| Oozing | 1 (2.8) | 73 (3.6) | 0 (0.0) | 44 (2.3) |
| Mild | 2 (5.6) | 51 (2.5) | 3 (10.0) | 57 (2.9) |
| Moderate | 0 (0.0) | 3 (0.1) | 0 (0.0) | 6 (0.3) |
| Severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Life Threatening | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Retroperitoneal** | | | | |
| None | 35 (97.2) | 2029 (99.9) | 30 (100.0) | 1946 (99.6) |
| Any | 1 (2.8) | 3 (0.1) | 0 (0.0) | 7 (0.4) |
| Oozing | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Mild | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| Moderate | 1 (2.8) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| Severe | 0 (0.0) | 1 (0.1) | 0 (0.0) | 4 (0.2) |
| Life Threatening | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| **Hematoma[f]** | | | | |
| None | 36 (0.0) | 2032 (100.0) | 28 (93.3) | 1778 (91.0) |
| Any | 0 (0.0) | 0 (0.0) | 2 (6.7) | 175 (9.0) |
| Oozing | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (0.3) |
| Mild | 0 (0.0) | 0 (0.0) | 1 (3.3) | 95 (4.8) |
| Moderate | 0 (0.0) | 0 (0.0) | 1 (3.3) | 69 (3.5) |
| Severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (0.3) |
| Life Threatening | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Hemoptysis | | | | |
| None | 36 (100.0) | 2016 (99.2) | 30 (100.0) | 1933 (99.0) |
| Any | 0 (0.0) | 16 (0.8) | 0 (0.0) | 20 (1.0) |
| Oozing | 0 (0.0) | 7 (0.3) | 0 (0.0) | 7 (0.4) |
| Mild | 0 (0.0) | 8 (0.4) | **0 (0.0)** | 12 (0.6) |
| Moderate | 0 (0.0) | 1 (0.1) | **0 (0.0)** | 1 (0.1) |
| Severe | 0 (0.0) | 0 (0.0) | **0 (0.0)** | **0 (0.0)** |
| Life Threatening | 0 (0.0) | 0 (0.0) | **0 (0.0)** | **0 (0.0)** |

**Table 8.1.6.5.2 Sub.jects** with tirofiban overdose (OD) in the phase II-III da (cont)[a].

| Any Bleeding Complication | Tirofiban alone | | Tirofiban +Heparin | |
|---|---|---|---|---|
| | With OD (n=36) | Overall Cohort[b] (n=2032) | With OD (n=30)[c] | Overall Cohort[b] (n=1953) |
| **Other** | | | | |
| None | 33 (91.7) | 1961 (96.5) | 29 (96.7) | 1873 (95.9) |
| Any | 3 (8.3) | 71 (3.5) | 1 (3.3) | 80 (4.1) |
| Oozing | 1 (2.8) | 30 (1.5) | 1 (3.3) | 31 (1.6) |
| Mild | 1 (2.8) | 17 (0.8) | 0 (0.0) | 24 (1.2) |
| Moderate | 0 (0.0) | 6 (0.3) | 0 (0.0) | 8 (0.4) |
| Severe | 0 (0.0) | 8 (0.4) | 0 (0.0) | 6 (0.3) |
| Life Threatening | 1 (2.8) | 10 (0.5) | 0 (0.0) | 7 (0.4) |
| **Unknown Site'** | | | | |
| **None** | 36 (100.0) | 1972 (97.0) | 26 (86.7) | 1908 (97.7) |
| Any | 0 (0.0) | 60 (3.0) | 4 (13.3) ‡ | 45 (2.3) |
| **Oozing** | 0 (0.0) | 20 (1.0) | 0 (0.0) | 1 (0.1) |
| **Mild** | 0 (0.0) | 23 (1.1) | 3 (10.0) | 16 (0.8) |
| Moderate | 0 (0.0) | 8 (0.4) | 0 (0.0) | 13 (0.7) |
| Severe | 0 (0.0) | 3 (0.1) | 0 (0.0) | 8 (0.4) |
| Life Threatening | 0 (0.0) | 0 (0.0) | (0 0 . 0 ) | 0 (0.0) |

a. Data from NDA 20-913, volume 7.2, ref. 35, page 841. This table contains counts of pati ts. Patients with lore than one bleeding complication in any one site are counted only once in that site.

b. Includes both non-overdose and overdose patients.

c. For one episode of bleeding, bleeding severity was not recorded.

d. In 6 patients in the overall tirofiban-alone cohort, a severity grade was not recorded. In 9 patients in the overall tirofiban + heparin cohort, a severity grade was not recorded.

e. 'Site Unknown' represents decreases in hematologic parameters considered clinically significant by the investigator, but that were not associated with overt bleeding. These events were reportable as bleeding complications, per data handling guidelines.

f. The site designation "hematoma" was restricted to the RESTORE trial and was largely localized to catheterization site bleeding.

8.1.7 Selected Adverse Events Collected from the Tirofiban Safety Database

This section will examine the incidence of selected adverse events in the safety database. These AEs have been chosen first because of adverse events identified from other members of the platelet IIb/IIIa receptor antagonists (see section 2.2.2), or because the data presented above for the overall safety of tirofiban suggests a possible association between a given adverse event and the administration of tirofiban. These adverse events including increased bleeding, neutropenia, and thrombocytopenia. Other adverse events will be included because of their importance to all drug development programs (LFT abnormalities). Finally, this section will summarize the incidence of AEs by race, sex, and age, as well as the interaction of selected drugs and disease states with tirofiban, as judged by the incidence of AEs.

For most of the data submitted as part of the NDA, the sponsor divided the heparin group into those associated with procedures, and those which were not. This issue was discussed in section 8.0.4.7 above.

8.1.7.1 Bleeding complications in the phase II-II database

Given that bleeding complications are the most common adverse events which occur during heparin-based therapies, and given the proposed mechanism of action for tirofiban, it is critical to examine the adverse events related to bleeding that occurred in the NDA database.

For the phase III trials, subjects were excluded from the trials if they had a recent history of bleeding disorders or were at increased risk for bleeding. The following categories of subjects were excluded in the PRISM-PLUS, PRISM, and RESTORE trials:

1. Recent (<1 year) or active bleeding disorder, including a history of gastrointestinal bleeding, or genitourinary bleeding of clinical significance (e.g., hematuria). Subjects with low hemoglobin (<11 g/dL) or hematocrit (<34%) were also excluded as a precautionary measure.
2. Known coagulopathy, platelet disorder, or history of thrombocytopenia. Subjects were also to be excluded for a platelet count of <150,000/mm$^3$.
3. Any confirmed persistent recording of systolic blood pressure exceeding 180 mmHg and/or diastolic blood pressure exceeding 110 mmHg at time of enrollment.
4. Any history of hemorrhagic cerebrovascular disease or active intracranial pathologic process within 1 year.
5. Traumatic or prolonged cardiopulmonary resuscitation within 2 weeks.
6. Subjects with a major surgical procedure within 1 month.
7. Subjects with severe physical trauma within 3 months.
8. History, symptoms or findings suggestive of aortic dissection.
9. Active peptic ulcer disease within 3 months.
10. Invasive procedures (except cardiac catheterization) within 14 days that would significantly increase the risk of hemorrhage (such as organ biopsy).
11. Probable pericarditis.
12. Presence of known significant (e.g., hemorrhagic) retinopathy.

Bleeding complications in each respective trial were tabulated from a "Bleeding Complications" case report form, which captured bleeding events reported either as a clinical adverse experience or a laboratory adverse experience on the "Adverse Experience" case report form. Clinically overt bleeding was captured according to the site of the bleeding on the "Bleeding Complications" form; in some cases postoperative bleeding was classified under site "Other" (in particular after coronary artery bypass surgery). "Unknown" was used if the patient had a laboratory adverse experience of a decreased hemoglobin/hematocrit, but no clinically overt bleeding could be identified by the investigator. The laboratory adverse experience of microscopic hematuria ("urine red blood cells increased") was captured on the "Bleeding Complications" form as GU/Hematuria "Oozing"; positive fecal occult blood (as a laboratory adverse experience) was captured as GI "Oozing."

Severity of bleeding was recorded based on the following defmitions:

Oozing: <50 cc blood loss.

Mild: Of no clinical consequence, not requiring transfusion, less than 250 cc blood loss.

Moderate: 250 to 500 cc observed blood loss.

Severe: >500 cc blood loss requiring transfusion replacement. Blood transfusions should not have been merely for augmentation of hematocrit.

Life-Threatening: (1) Intracranial bleeding; (2) gastro-intestinal or other internal or external bleeding causing hypotension.

8.1.7.1 Bleeding complications in the phase II-II database **(cont)**

All bleeding complications from initiation of study drug through the 24-hour period after study drug cessation were captured; each site was to be noted and evaluated separately. Transfusions, which were also captured, were to be ascribed to the site that was most likely to have contributed to the need for transfusion.

Each protocol also had a unique definition of "major" bleeding, as determined by the individual Steering Committees for the respective studies. These definitions are shown below. Any single criterion within the respective protocol would qualify the patient to be classified as having a "major" bleed.

1. PRISM-PLUS: (1) hemoglobin drop >4.0 g/dL;
   (2) transfusion of two or more units of blood;
   (3) need for corrective surgery;
   (4) intracranial hemorrhage; or
   (5) retroperitoneal hemorrhage.

2. PRISM: (1) hemoglobin drop >3.5 g/dL;
   (2) transfusion of two or more units of blood;
   (3) need for corrective surgery;
   (4) intracranial hemorrhage; or
   (5) retroperitoneal hemorrhage.

3. RESTORE: (1) hemoglobin drop >5.0 g/dL;
   (2) transfusion of two or more units of blood;
   (3) need for corrective surgery;
   (4) intracranial hemorrhage; or
   (5) retroperitoneal hemorrhage.

To allow more uniform comparison between the protocols to studies published in the literature, analyses of bleeding complications were also performed using the criteria from the trials of Thrombolysis in Myocardial Infarction (TIMI criteria).

The TIMI criteria for "Major" and "Minor" bleeding, and "Loss, No Site," are:

TIMI Major: (1) hemoglobin drop >50 g/L (with or without an identified site);
(2) intracranial hemorrhage; or
(3) cardiac tamponade.

TIMI Minor: (1) hemoglobin drop >30 g/L with bleeding from a known site;
(2) spontaneous gross hematuria, hematemesis or hemoptysis.

TIMI "Loss, No Site": hemoglobin drop >40 g/L with no site identified.

With respect to transfusions, the groups within each study were compared with respect to the percentage of subjects receiving a transfusion of any type as well as the percentage of subjects receiving a specific type of transfusion (e.g., whole blood, fresh frozen plasma, packed red blood cells, cryoprecipitate, platelets). Subjects with more than one transfusion counted only once in the analysis of transfusion of any type; however, a patient who had multiple transfusions of different types counted in all applicable analyses.

Following a summary of the incidence of bleeding adverse events from the combined database, bleeding in each of the phase III trials will be examined individually.

**8.1.7.1a Bleeding-related deaths in the phase II-III database**

The first table summarizes the number of deaths associated with clinically significant bleeding in the phase III trials. When expressed as a percentage of deaths in each category, there was a higher percentage of the tirofiban + heparin subject deaths associated with clinically significant bleeding than either tirofiban or heparin alone. The last column lists the number of subjects who had bleeding develop during or shortly (<1 day) after receiving study drug infusion, which lead ultimately to death.

Table 8.1.7.1a.1 Deaths associated with Bleeding from the PRISM-PLUS, PRISM, and RESTORE trials".

| Treatment Group | Total Number of Deaths | Associated with Bleeding | Bleeding Temporally Associated with Study Drug Infusion |
|---|---|---|---|
| Tirofiban (n=2032) | 61 | 5 (8%) | 3 (4.9%) |
| Tirofiban +Heparin (n=1953) | 37 | 9 (24%) | 4 (10.8%) |
| Heparin (n=3546) | 106 | 16 (14%) | 5 (4.7%) |
| Total | 204 | 30 (15%) | 12 (5.9%) |

a. Data comes from inspection of individual patient death summaries (see section 14.0) and CRFs by medical reviewer.

The following deaths were associated with clinically significant bleeding. Details of the individual deaths can be found in the death summary, appendix 2. The subjects in bold type had their bleeding AE during study drug administration. While the numbers are small, intracranial, retroperitoneal, mediastinal, and pericardial bleeding AEs were seen in all three treatment groups.

Table 8.1.7.1 a.2 List of deaths associated with bleeding adverse events from the PRISM-PLUS, PRISM, and RESTORE trials[a].

| Subject # | Bleeding adverse event |
|---|---|
| **Tirofiban** | |
| **006-044 AN 6250** | **GI hemorrhage, mesenteric ischemia** |
| **006-050 AN 6547** | 'Major bleeding' 4 days after D/C of study drug |
| 011-023 AN 2518 | DIC 7 days after D/C of study drug |
| **011-114 AN 5597** | **Cardiac tamponade** |
| **011-155 AN 6552** | **Melena** |
| **Tirofiban +Heparin** | |
| 006-095 AN 1567 | Cardiac tamponade 7 days after D/C of study drug |
| 006-049 AN 6591 | 'Excessive blood loss' >4 days after D/C of study drug |
| 006-048 AN 7243 | Groin site bleeding requiring transfusion 2 days after study drug D/C |
| **006-092 AN 7483** | **Hemoperitoneum** |
| **006-102 AN 5604** | Thoracic aortic dissection, starting 1 day after study drug D/C |
| **013-003 AN 1286** | **Intracranial hemorrhage** |
| **013-021 AN 1777** | **Retroperitoneal hemorrhage** |
| **013-021 AN 1809** | **Retroperitoneal hemorrhage & cardiac tamponade** |
| 013-003 AN 3144 | GI hemorrhage starting after D/C of study drug |
| **Heparin** | |
| **006-034 AN 1067** | Heme-arthrosis 20 days after study drug D/C |
| **006-084 AN 1234** | **Retroperitooeal hemorrhage** |
| **006-057 AN 5310** | **Groin hematoma, pulmonary embolism** |
| **006-059** AN 6155 | 'Uncontrolled bleeding' starting 9 days after study drug D/C |
| **006-043** AN 6676 | Retroperitoneal hemorrhage developing 14 days after study drug D/C |
| **006-034 AN 698 l** | Pulmonary hemorrhage after Swann-Ganz misplacement 21 days after study drug D/C |
| 006-094 AN 7613 | Coronary artery dissection after stent placement 3 days after study drug D/C |
| 011-092 AN 1320 | Intracranial hemorrhage 9 days after D/C of study drug |
| 0 1 l-092 AN 2467 | Mediastinal bleeding 11 days after D/C of study drug |
| 01 l-065 AN 3280 | Hemorrhagic CVA 14 days after D/C of study drug |
| **011-061 AN 5160** | ***Groin hematoma requiring transfusion*** |
| 011-072 AN 7001 | DIC 6 days after D/C of study drug, following a CABG |
| 013-045 AN 1425 | GI hemorrhage following sepsis, 6 days after drug D/C |
| **013-030 AN 1445** | **Retroperitoneal hemorrhage** |
| **013-020 AN 2932** | **Groin hematoma** |

a. Data comes from inspection of individual patient death summaries (see section 14.0) and CRFs by medical reviewer.

**8.1.7.1b** Bleeding Serious adverse events **(SAEs)** in the phase II-III safety database

The table below shows the number and percentage of subjects who reported clinical serious adverse experiences (SAEs) (≥0.5%) associated with bleeding, by body system. The serious adverse events noted during each trial are summarized to be found in the individual trial reviews. Note the increased incidence of SAEs associated with GI hemorrhage in the tirofiban +heparin and tirofiban groups, relative to their respective heparin comparison groups and with the total heparin group.

Table 8.1.7.1b.1 Bleeding-related SAEs in the tirofiban phase II-III safety database[a].

| Body System/ SAE | Tirofiban + Heparin n=1953 | Heparin/ Procedures n=1887 | Tirofiban n=2032 | Heparin/ No Procedures n=1659 | Total Heparin Alone n=3546 |
|---|---|---|---|---|---|
| **Cardiovascular System** | 231 (11.8%) | 210 (11.1%) | 241 (11.9%) | 179 (10.8%) | 389 (11.0%) |
| Bleeding, postoperative | 15 (0.8%) | 15 (0.8%) | 13 (0.6%) | 5 (0.3%) | 20 (0.6%) |
| Dissection, Coronary Artery | 35 (1.8%) | 34 (1.8%) | 3 (0.1%) | 1 (0.1%) | 35 (1.0%) |
| **Digestive System** | 29 (1.5%) | 17 (0.9%) | 33 (1.6%) | 14 (0.8%) | 31 (0.9% |
| Hemorrhage, gastrointestinal | 11 (0.6%) | 2 (0.1%) | 9 (0.4%) | 0 (0%) | 2 (<0.1) |

a. Data from NDA volume 1.37, Table D-60 and electronic datasets.

**8.1.7.1c** Bleeding-related discontinuations in the phase II-II database

As seen in the table below, more subjects in the tirofiban groups were discontinued from study drug due to bleeding (3.6% in Tirofiban + Heparin, 1 .1% in Heparin alone, 0.7% in combined Heparin alone). The majority of these bleeding events were related to post-operative bleeding and hematoma formation. Note, also, that 9 subjects in the two tirofiban groups were discontinued for Respiratory system bleeding versus 1 of the subjects receiving heparin. For the shaded SAEs, there is a ≥2X difference between one of the tirofiban groups and its respective heparin group with regard to incidence.

Table 8.1.7.1c.1 Clinical bleeding AEs leading to subject discontinuation, collected in the tirofiban phase II-III safety database[a].

| Body System/ SAE | Tirofiban + Heparin n=1953 | Heparin/ Procedures n=1887 | Tirofiban n=2032 | Heparin/ No Procedures n=1659 | Total Heparin Alone n=3546 |
|---|---|---|---|---|---|
| **Total # with bleeding AEs leading to discontinuation** | 71 (3.6%) | 19 (1.0%) | 22 (1.1%) | 6 (0.4%) | 25 (0.7%) |
| **Cardiovascular System** | 41 (2.1%) | 13 (0.7%) | 3 (0.1%) | 1 (0.1%) | 14 (0.4%) |
| Bleeding, postoperative | 24 (1.2%) | 5 (0.3%) | 1 (<0.1%) | 0 (0%) | 5 (0.1%) |
| Hematoma | 15 (0.8%) | 5 (0.3%) | 0 (0%) | 0 (0%) | 5 (0.1%) |
| **Digestive System** | 19 (1.0%) | 4 (0.2%) | 11 (0.5%) | 1 (0.1%) | 5 (0.1%) |
| **Hemic & Lymphatic System** | See labs | | | | |
| **Respiratory System** | 5 (0.3%) | 0 (0%) | 4 (0.2%) | 1 (0.1%) | 1 (<0.1%) |
| **Dermatologic System** | 2 (0.1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Urogenital System** | 11 (0.6%) | 3 (0.2%) | 4 (0.2%) | 3 (0.2%) | 6 (0.4%) |

a. Data from NDA volume 1.37, Table D-49 and electronic datasets.

With regard to lab-related AEs leading to discontinuations, more subjects in the tirofiban +heparin group were discontinued due to decreased platelets than the comparator heparin group: 10/1934 (0.5%) for tirofiban +heparin; 2/1869 (0.1%) for the heparin/procedure group. No significant difference in any other lab abnormality that lead to discontinuation, including changes in hematocrit, was detected.

**8.1.7.1d** Bleeding **AEs** in the phase II-III safety database

Bleeding within all body systems was increased in the groups treated with tirofiban, relative to the heparin-only group. Next, the adverse events related to bleeding are repeated from above to facilitate comparisons. The largest difference relative to the heparin group (expressed as % change) occurred in Digestive and Respiratory system bleeding AEs. The tirofiban +heparin group also had and increased incidence of bleeding AEs in the Cardiovascular, Hemic & Lymphatic, and Skin & Appendages systems.

The shaded boxes represents AEs where there is ≥2X difference between one of the two tirofiban groups and either its respective heparin group, or the total heparin group.

Table 8.1.7.1d.1 Bleeding adverse events in the phase II-III trials of tirofiban from NDA 20-912[a].

| Bleeding AEs | Tirofiban + Heparin n=1953 | Heparin/ Procedures n=1887 | Tirofiban n=2032 | Heparin/ No Procedures n=1659 | Total Heparin Alone n=3546 |
|---|---|---|---|---|---|
| Subjects with bleeding clinical AE | 1021 (52.3%) | 733 (38.8%) | 424 (20.9%) | 143 (8.6%) | 876 (24.7%) |
| Subjects without bleeding clinical AE | 932 (47.7%) | 1154 (61.2%) | 1608 (79.1%) | 1516 (91.4%) | 2670 (75.2%) |
| Body as a whole | 1 (0.1%) | 1 (0.1%) | 10 (0.5%) | 9 (0.5%) | 10 (0.3%) |
| Cardiovascular System | 844 (43.2%) | 616 (32.6%) | 245 (12.1%) | 86 (5.2%) | 702 (19.8%) |
| Bleeding, postoperative | 659 (33.7%) | 468 (24.8%) | 139 (6.8%) | 34 (2.0%) | 502 (14.1%) |
| Extravasation | 8( 0.4%) | 3 (0.2%) | 13 (0.6%) | 4 (0.2%) | 7 (<0.1%) |
| Hematoma | 206 (10.5%) | 125 (6.6%) | 63 (3.1%) | 26 (1.6%) | 151 (4.2%) |
| Hemorrhage | 24 (1.2%) | 39 (2.1%) | 11 (0.5%) | 3 (0.2%) | 42 (1.2%) |
| Hemorrhage, IV site | 105 (5.4%) | 77 (4.1%) | 61 (3.0%) | 20 (1.2%) | 97 (2.7%) |
| Digestive System | 96 (4.9%) | 29 (1.5%) | 53 (2.6%) | 13( 0.8%) | 42 (1.2%) |
| Hematemesis | 17 (0.9%) | 6 (0.3%) | 4 (0.2%) | 0 (0.0%) | 6 (0.2%) |
| Hemorrhage, gastrointestinal | 18 (0.9%) | 4 (0.2%) | 11 (0.5%) | 6 (0.4%) | 10 (0.3%) |
| Hemorrhage, gingival | 19 (1.0%) | 3 (0.2%) | 11 (0.5%) | 3 (0.2%) | 6 (0.2%) |
| Hemorrhage, oral | 28 (1.4%) | 5 (0.3%) | 8 (0.4%) | 0 (0.0%) | 5 (0.2%) |
| Hemic and Lymphatic System | 4 (0.2%) | 1 (0.1%) | 5 (0.2%) | 0 (0.0%) | 1 (<0.1%) |
| Respiratory System | 125 (6.4%) | 33 (1.7%) | 143 (7.0%) | 21 (1.3%) | 54 (1.5%) |
| Epistaxis | 109 (5.6%) | 20 (1.1%) | 130 (6.4%) | 18 (1.1%) | 38 (1.1%) |
| Hemoptysis | 23 (1.2%) | 11 (0.6%) | 18 (0.9%) | 3 (0.2%) | 14 (0.4%) |
| Skin and Skin Appendage | 222 (11.4%) | 154 (8.2%) | 43 (2.1%) | 5 (0.3%) | 159 (4.5%) |
| Ecchymosis | 217 (11.1%) | 153 (8.1%) | 40 (2.0%) | 5 (0.3%) | 158 (4.5%) |
| Special Senses | I 3 (0.2%) | I 0 (0.0%) | I 3 (0.1%) | 2 (0.1%) | 2 (<0.1%) |
| Urogenital | 73 (3.7%) | 49 (2.6%) | 29 (1.4%) | 18 (1.1%) | 67 (1.9%) |
| Hematuria | 67(3.4%) | 42 (2.2%) | 26 (1.3%) | 17 (1.0%) | 59 (1.7%) |

a. Data from NDA volume 1.2, Table C-39 and electronic datasets.

The individual sites of bleeding were also summarized by the sponsor for all three studies, ranked according to severity by the scale discussed at the beginning of this section (8.1.7.1). The results are shown below. The sites of bleeding for individual trials are summarized in the appropriate sections below. Note that this table includes the number of retroperitoneal & intracranial bleeds. Shaded AEs represent those in which the tirofiban and related heparin groups differ by >2% (greater for tirofiban) or ≥2X.

## 8.1.7.1d Bleeding AEs in the phase II-III safety database (cont)

Table 8.1.7.1d.2 Bleeding adverse events grouped according to severity and by site in the phase II-III trials of tirofiban from NDA 20-912[a].

| Bleeding AEs by Site | Tirofiban+Heparin (N=1953) | | Heparin/Procedures (N=1887) | | Tirofiban (N=2032) | | Heparin/ No Procedures (N=1659) | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| **Patients with no Bleeding AE** | 868 | 44.4 | 1100 | 58.3 | 1394 | 68.6 | 1373 | 82.8 |
| **Patients with Any Bleeding AE** | 1085 | 55.6 | 787 | 41.7 | 638 | 31.4 | 286 | 17.2 |
| **Bleeding, Catheter Site** | | | | | | | | |
| Any | 661 | 33.8 | 460 | 24.4 | 155 | 7.6 | 37 | 2.2 |
| Oozing | 468 | 23.9 | 317 | 16.8 | 72 | 3.5 | 17 | 1.0 |
| Mild | 126 | 6.4 | 106 | 5.6 | 52 | 2.6 | 10 | 0.6 |
| Moderate | 56 | 2.9 | 32 | 1.7 | 23 | 1.1 | 6 | 0.4 |
| Severe | 10 | 0.5 | 5 | 0.3 | 6 | 0.3 | 3 | 0.2 |
| Life-Threatening | 1 | 0.1 | 0 | 0.0 | 2 | 0.1 | 1 | 0.1 |
| **Bleeding, GI** | | | | | | | | |
| Any | 124 | 6.3 | 69 | 3.7 | 122 | 6.0 | 47 | 2.8 |
| Oozing | 43 | 2.2 | 29 | 1.5 | 57 | 2.8 | 27 | 1.6 |
| Mild | 53 | 2.7 | 33 | 1.7 | 43 | 2.1 | 14 | 0.8 |
| Moderate | 19 | 1.0 | 5 | 0.3 | 12 | 0.6 | 3 | 0.2 |
| Severe | 5 | 0.3 | 1 | 0.1 | 5 | 0.2 | 3 | 0.2 |
| Life-Threatening | 4 | 0.2 | 1 | 0.1 | 5 | 0.2 | 0 | 0.0 |
| **Bleeding, GU/Hematuria[b]** | | | | | | | | |
| Any | 278 | 14.2 | 184 | 9.8 | 214 | 10.5 | 112 | 6.8 |
| Oozing | 71 | 3.6 | 57 | 3.0 | 108 | 5.3 | 66 | 4.0 |
| Mild | 162 | 8.3 | 99 | 5.2 | 95 | 4.7 | 38 | 2.3 |
| Moderate | 40 | 2.0 | 24 | 1.3 | 10 | 0.5 | 7 | 0.4 |
| Severe | 3 | 0.2 | 4 | 0.2 | 1 | 0.1 | 1 | 0.1 |
| Life-Threatening | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Bleeding, Intracranial** | | | | | | | | |
| Any | 1 | 0.1 | 3 | 0.2 | 2 | 0.1 | 2 | 0.1 |
| Oozing | 0 | 0.0 | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 |
| Mild | 0 | 0.0 | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 |
| Moderate | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 |
| Severe | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Life-Threatening | 1 | 0.1 | 2 | 0.1 | 0 | 0.0 | 2 | 0.1 |
| **Bleeding, IV Site** | | | | | | | | |
| Any | 117 | 6.0 | 86 | 4.6 | 110 | 5.4 | 48 | 2.9 |
| Oozing | 67 | 3.4 | 50 | 2.6 | 67 | 3.3 | 26 | 1.6 |
| Mild | 42 | 2.2 | 33 | 1.7 | 40 | 2.0 | 18 | 1.1 |
| Moderate | 8 | 0.4 | 3 | 0.2 | 3 | 0.1 | 3 | 0.2 |
| Severe | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Life-Threatening | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 0.1 |
| **Bleeding, Oral/Mouth** | | | | | | | | |
| Any | 51 | 2.6 | 14 | 0.7 | 20 | 1.0 | 5 | 0.3 |
| Oozing | 18 | 0.9 | 5 | 0.3 | 12 | 0.6 | 1 | 0.1 |
| Mild | 31 | 1.6 | 5 | 0.3 | 7 | 0.3 | 3 | 0.2 |
| Moderate | 2 | 0.1 | 4 | 0.2 | 1 | 0.1 | 1 | 0.1 |
| Severe | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Life-Threatening | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

## 8.1.7.1d Bleeding AEs in the phase II-III safety database (cont

Table 8.1.7.1d.2 Bleeding complications grouped according to severity and by site in the phase II-III trials of tirofiban from NDA 20-912 (cont)[a].

| Bleeding by Site | Tirofiban+Heparin (N=1953) | | Heparin/Procedures (N=1887) | | Tirofiban (N=2032) | | Heparin/No Procedures (N=1659) | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| **Bleeding, Other[b]** | | | | | | | | |
| Any | 80 | 4.1 | 41 | 2.2 | 71 | 3.5 | 20 | 1.2 |
| Oozing | 31 | 1.6 | 8 | 0.4 | 30 | 1.5 | 6 | 0.4 |
| Mild | 24 | 1.2 | 13 | 0.7 | 17 | 0.8 | 4 | 0.2 |
| Moderate | 8 | 0.4 | 12 | 0.6 | 6 | 0.3 | 4 | 0.2 |
| Severe | 6 | 0.3 | 4 | 0.2 | 8 | 0.4 | 2 | 0.1 |
| Life-Threatening | 7 | 0.4 | 3 | 0.2 | 10 | 0.5 | 4 | 0.2 |
| **Bleeding, Retroperitoneal** | | | | | | | | |
| Any | 7 | 0.4 | 4 | 0.2 | 3 | 0.2 | 1 | 0.1 |
| Oozing | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Mild | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Moderate | 1 | 0.1 | 0 | 0.0 | 1 | 0.1 | 1 | 0.1 |
| Severe | 4 | 0.2 | 1 | 0.1 | 1 | 0.1 | 0 | 0.0 |
| Life-Threatening | 1 | 0.1 | 3 | 0.2 | 1 | 0.1 | 0 | 0.0 |
| **Bleeding, Unknown[b]** | | | | | | | | |
| Any | 45 | 2.3 | 58 | 3.1 | 60 | 3.0 | 34 | 2.0 |
| Oozing | 1 | 0.1 | 7 | 0.4 | 20 | 1.0 | 18 | 1.1 |
| Mild | 16 | 0.8 | 30 | 1.6 | 23 | 1.1 | 11 | 0.7 |
| Moderate | 13 | 0.7 | 12 | 0.6 | 8 | 0.4 | 1 | 0.1 |
| Severe | 8 | 0.4 | 6 | 0.3 | 3 | 0.1 | 4 | 0.2 |
| Life-Threatening | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 |
| **Hematoma[f]** | | | | | | | | |
| Any | 175 | 9.0 | 112 | 5.9 | 0 | 0.0 | 0 | 0.0 |
| Oozing | 5 | 0.3 | 2 | 0.1 | 0 | 0.0 | 0 | 0.0 |
| Mild | 95 | 4.9 | 71 | 3.8 | 0 | 0.0 | 0 | 0.0 |
| Moderate | 69 | 3.5 | 35 | 1.9 | 0 | 0.0 | 0 | 0.0 |
| Severe | 6 | 0.3 | 3 | 0.2 | 0 | 0.0 | 0 | 0.0 |
| Life-Threatening | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 |
| **Hemoptysis** | | | | | | | | |
| Any | 20 | 1.0 | 9 | 0.5 | 16 | 0.8 | 3 | 0.2 |
| Oozing | 7 | 0.4 | 3 | 0.2 | 7 | 0.3 | 1 | 0.1 |
| Mild | 12 | 0.6 | 6 | 0.3 | 8 | 0.4 | 2 | 0.1 |
| Moderate | 1 | 0.1 | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 |
| Severe | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Life-Threatening | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Epistaxis[b]** | | | | | | | | |
| Any | 107 | 5.5 | 21 | 1.1 | 127 | 6.3 | 17 | 1.0 |
| Oozing | 44 | 2.3 | 14 | 0.7 | 73 | 3.6 | 10 | 0.6 |
| Mild | 57 | 2.9 | 7 | 0.4 | 51 | 2.5 | 5 | 0.3 |
| Moderate | 6 | 0.3 | 0 | 0.0 | 3 | 0.1 | 1 | 0.1 |
| Severe | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Life-Threatening | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

a Data from sponsor to medical reviewer directly. Data shown as number of subjects (% of total subjects) with bleeding at specifie site.

b. Intensity was not reported for a total of 23 patients for the following bleeding sites: GU/Hematuria (2 patients), Other (5 patients), Unknown (15 patients), and Epistaxis (1 patient). These 23 patients are not reported in the individual intensity listings (Oozing, Mild, Moderate, Severe or Life-Threatening; however, these patients are counted in their respective overall counts (Any).

e. 'Site Unknown' represents decreases in hematologic parameters considered clinically significant by the investigator, but that were not associated with overt bleeding. These events were reportable as bleeding complications, per data handling guidelines.

f. The site designation 'hematoma' was restricted to the RESTORE trial and was largely localized to catheterization site bleeding.

**8.1.7.1e** Other measures ofbleeding in the phase II-III safety database

**8.1.7.1e.0** Time-to-Bleeding Analysis

The sponsor performed an analysis of the incidence of bleeding up to 24 and 48 hours after completing administration of study drug for the PRISM-PLUS trial. An larger analysis of the association between the duration of study drug administration and the risk of bleeding for the entire safety database is included in appendix thirteen, to be performed by the sponsor, will be submitted as an addendum to this review when it is available.

The sponsor was asked to provide information regarding the bleeding AEs in the following groups:

1. Overall rate of bleeding for 24 and 48 hours after completion of study drug administration;
2. Rate of bleeding in subjects with no cardiac interventions during initial hospitalization; and
3. Rate of bleeding in subjects with cardiac interventions during initial hospitalization.

As discussed in section 8.0, all bleeding complications from initiation of study drug through the 24-hour period after study drug cessation were captured in the safety database, including the site and severity of bleeding.

The first table shows the incidence of bleeding events up to 24 hours after completion of study drug for subjects who received study drug in PRISM-PLUS. Therapy with tirofiban plus heparin was associated with an increased incidence of bleeding events. This table should be compared with the overall incidence of bleeding at any time during the PRISM-PLUS trial (table 6.2.1.13.2.6, p. 99). As before, subjects in the tirofiban +heparin group (T+H) had a higher incidence of bleeding events when compared with the heparin-alone group (H).

Table 8.1.7.1e.0.1 Bleeding episodes up to 24 hours after study drug cessation in subjects who received study drug" in the PRISM-PLUS trial.

| Site/ Severity n(%) | Tirofiban + Heparin[b] (N=766) | Heparin" (N=789) | p-value T + H vs. H |
|---|---|---|---|
| **Any Site** | | | **< 0.001** |
| Any | 338 (44.1%) | 450 (57.0%) | |
| Oozing | 171 (22.3%) | 151 (19.1%) | |
| Mild | 193 (25.2%) | 141 (17.9%) | |
| Moderate | 48 (6.3%) | 39 (4.9%) | |
| Severe | 14 (1.8%) | 6 (0.8%) | |
| Life-Threatening | 1 (0.1%) | 1 (0.1%) | |

a. Data from sponsor, **not** independently verified by the FDA.

b. Total number of patients per group do not add up since severity of tbe bleeding episode is missing for 1 patient in each of the treatment groups.

The next table evaluates bleeding complications in the small number of patients who did not undergo any invasive medical procedures during the initial hospitalization in the PRISM-PLUS trial. Subjects in the tirofiban plus heparin group had a small increase in the incidence of bleeding events.

Table 8.1.7.1e.0.2 Bleeding episodes in subjects who did not undergo invasive procedures in the PRISM-PLUS trial".

| Site/ Severity n(%) | Tirofiban + Heparin (N=72) | Heparin (N=80) | p-value T + H vs. H |
|---|---|---|---|
| **Any Site** | | | 0.095 |
| Any | 42 (58.3%) | 56 (70.0%) | |
| Oozing | 9 (12.5%) | 10 (12.5%) | |
| Mild | 13 (18.1%) | 10 (12.5%) | |
| Moderate | 6 (8.3%) | 2 (2.5%) | |
| Severe | 2 (2.8%) | 0 (0%) | |
| Life-Threatening | 0 (0%) | 2 (2.5%) | |

a. Data from sponsor, not independently verified by the FDA

The next table summarizes the first 48 hours of the study and prior to cardiac procedures. Remember that the PRISM-PLUS subjects were to had a protocol-specified angiography after 48-96 hours. Again, therapy with tirofiban plus heparin resulted in a small increase in the incidence of bleeding events compared to therapy with heparin alone.

Table 1.7.1e.0.3 Bleeding within 48 hours of study entry, prior to cardiac procedures in PRISM-PLUS".

| Site/ Severity n(%) | Tirofiban + Heparin[b] (N=72) | Heparin[b] (N=80) | p-value T + H vs. H |
|---|---|---|---|
| **Any Site** | | | **< 0.001** |
| Any | 533 (69.0%) | 652 (81.8%) | |
| Oozing | 105 (13.6%) | 72 (9.0%) | |
| Mild | 107 (13.8%) | 60 (7.5%) | |
| Moderate | 23 (3.0%) | 11 (1.4%) | |
| Severe | 4 (0.5%) | 0 (0%) | |
| Life-Threatening | 0 (0%) | 0 (0%) | |

a. Data from sponsor, not independently verified by the FDA.
b. Total number of patients per group do not add up since seventy of the bleeding episode is missing for 3 subjects

The final table shows the incidence of bleeding complications in patients who underwent invasive cardiac procedures during the initial hospitalization. This includes a large fraction of the subjects in both groups: 701/773 randomized subjects in the tirofiban +heparin group (90.6%) and 717/797 randomized subjects in the heparin group (89.9%). Compared to the subjects who did not undergo cardiac procedures during the initial hospitalization (table 8.1.7.1e.0.2 above) and to patients during prior to their interventions (table 8.1.7.1e.0.3 above), there is an increase in the incidence of bleeding episodes in both the tirofiban plus heparin and heparin-alone groups. This included an increase in the incidence of severe and life-threatening bleeding events.

Table 8.1.7.1e.0.4 Bleeding in subjects who underwent cardiac procedures in PRISM-PLC [a]

| Site/ Severity n(%) | Tirofiban + Heparin[b] (N=701) | Heparin[b] (N=717) | p-value T + H vs. H |
|---|---|---|---|
| Any Site | | | < 0.001 |
| Any | 298 (42.5%) | 400 (55.8%) | |
| Oozing | 162 (23.1%) | 139 (19.4%) | |
| Mild | 175 (25.0%) | 129 (18.0%) | |
| Moderate | 44 (6.3%) | 34 (4.7%) | |
| Severe | 15 (2.1%) | 11 (1.5%) | |
| Life-Threatening | 6 (0.9%) | 3 (0.4%) | |

a. Data from sponsor, not independently verified by the FDA.
b. Total number of patients per group do not add up since severity of the bleeding episode is missing for 1 patient in each of the treatment groups.

Finally, as described in the methods portion of this analysis, adverse experience reporting occurred during study drug infusion and up to 24 hours following drug cessation (with the exception of serious adverse experiences, which were collected for 30 days following randomization). Thus, there are no data on the incidence of bleeding-related adverse events in patients who underwent procedures after study drug cessation.

8.1.7.1e.l Transfusions in the combined Phase II-III database

In the phase II-III database, the groups were compared with respect to the percentage of subjects requiring a transfusion of any type, the percentage requiring a transfusion of a specific type (whole blood, FFP, PRBCs, cryoprecipitates, and platelets), and the total number of units of PRBCs. Subjects with more than one transfusion counted only once in the analysis of transfusions of any type; however, a patient who had multiple transfusions of different types counted in all applicable analyses. In addition, subjects with multiple transfusions of the same type counted only once in the analysis of the percent of subjects requiring a transfusion, but the number of units transfused were summed. As in the analysis of bleeding complications, all subjects who received study drug or placebo were included in this analysis.

Protocols #005 and #008 had no bleeding complications that required transfusions. Protocol #007 had two subjects that required transfusions, Two units were transfused in each patient (AN 0 17 and AN 24 1). Note: the case report forms for Protocol #007 did not capture the type of transfusion. For purposes of integration into the overall transfusion summary below, the assumption is made that these subjects were transfused PRBCs.

The following table integrates the transfusion requirements across the phase II - III database. A higher percentage of tirofiban +heparin subjects required transfusion of any kind than the heparin/ procedure group (3.9% vs. 2.8%). The tirofiban group also had a higher frequency of any transfusion than the heparin/ no procedure group (2.8% vs. 1.4%). The incidence of PRBC transfusion was also higher in the tirofiban groups.

Table 8.1.7. le. 1.1 Overall transfusion requirements in the phase II-III safety database[a,b].

| Type of Transfusion | Tirotiban + Heparin (N=1953) | Heparin/ Procedure (N=1887) | Tirofiban (N=2032) | Heparinf No Procedure (N=1659) |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) |
| **Any Transfusion** | | | | |
| No | 1876 (96.1%) | 1838 (97.4%) | 1976 (97.2%) | 1636 (98.6%) |
| Yes | 77 (3.9%) | 49 (2.6%) | 56 (2.8%) | 23 (1.4%) |
| **Whole Blood** | | | | |
| No | 1947 (99.7%) | 1883 (99.8%) | **2026 (99.7%)** | **1657 (99.9%)** |
| **Yes** | **6 (0.3%)** | **4 (0.2%)** | **6 (0.3%)** | **2 (0.1%)** |
| **FFP** | | | | |
| **No** | **1944 (99.5%)** | **1879 (99.6%)** | **2019 (99.4%)** | **1655 (99.8%)** |
| **Yes** | **9 (0.5%)** | **8 (0.4%)** | **13 (0.6%)** | **4 (0.2%)** |
| **PRBC** | | | | |
| No | 1882 (96.4%) | 1842 (97.6%) | 1984 (97.6%) | 1639 (98.8%) |
| Yes | 71 (3.6%) | 45 (2.4%) | 48 (2.4%) | 20 (1.2%) |
| **Cryoprecipitates** | | | | |
| **No** | 1952 (99.9%) | **1885 (99.9%)** | **2031 (99.95%)** | **1659** (100.0%) |
| Yes | 1 (0.1%) | **2** (0.1%) | 1 (0.05%) | 0 (0.0%) |
| **Platelets** | | | | |
| **Nil** | 1947 (99.7%) | 1881 (99.7%) | 2019 (99.4%) | 1655 (99.8%) |
| Yes | **6 (0.3%)** | **6 (0.3%)** | **13 (0.6%)** | **4 (0.2%)** |
| **Other** | | | | |
| **No** | **1948 (99.7%)** | **1885 (99.9%)** | **2029 (99.9%)** | **1658 (99.9%)** |
| **Yes** | **5 (0.3%)** | **2** (0.1%) | **3 (0.1%)** | 1 (0.1%) |

**a.** The case report forms for Protocol 007 did not capture the type of transfusion data Therefore, since the majority of the reported transfusions in the Phase III studies were reported as PRBCs, these patient's transfusion (AN 017 and AN 241) are shown in their appropriate treatment group under PRBC.

b. Data from sponsor at request of medical reviewer.

8.1.7.1e.2 Occurrence of major and minor bleeding in the combined Phase II-III database

The table below summarizes the occurrence of either protocol-specified or TIMI-class major bleeding.

The TIM1 major bleeding criteria were: 1) hemoglobin drop ≥5 g/dl; 2) intracranial bleed or cardiac tamponade. The TIM1 minor bleeding criteria were. 1) hemoglobin drop >3 g/dl from a known site; 2) spontaneous gross hematuria, hematemesis; or hemoptysis; and 3) does not meet criteria for TIMI major bleed. Additionally, the tables below include only those subjects who did not have a bleeding event associated with CABG.

There was a higher incidence of TIMI-major and minor bleeding in the tirofiban+heparin group, compared to heparin alone, in both the RESTORE and PRISM-PLUS trials. Protocol-specified major bleeding was also increased in the tirofiban +heparin arm in all three trials, especially the RESTORE trial.

Table 8.1.7.1e.2.1 Occurrence of major bleeding in the PRISM-PLUS, PRISM, and RESTORE trials".

| | Tirofiban | Tirofiban +Heparin | Heparin | p-value |
|---|---|---|---|---|
| PRISM-PLUS | | | | |
| Protocol-specified major bleeds | 18 (5.2%) | 31 (4.0%) | 24 (3.5%) | 0.34 |
| TIMI Major bleeds | 9 (2.6%) | 11 (1.4%) | 6 (0.8%) | 0.23[b] |
| TIMI Minor bleeds | 35 (10.1%) | 81 (10.5%) | 64 (0.8%) | -- |
| PRISM | | | | |
| Protocol-specified major bleeds | 21 (1.3%) | | 14 (0.9%) | 0.31 |
| TIMI Major bleeds | 7 (0.4%) | | 6 (0.4%) | 0.91[b] |
| TIMI Minor bleeds | 33 (2.0%) | | 31 (1.9%) | -- |
| RESTORE | | | | |
| Protocol-specified major bleeds | | 57 (5.3%) | 40 (2.7%) | 0.096 |
| TIMI Major bleeds | | 24 (2.2%) | 17 (1.6%) | 0.344[b] |
| TIMI Minor bleeds | | 129 (12.0%) | 67 (6.3%) | -- |

a. Data from individual trial reports.

b. p values for TIMI-class bleeding taken from analysis of all bleeding, including loss-no site' category which is not shown here for purposes of comparison with other trials.

**8.1.7.1e.3** Comparison of the incidence of major bleeding in the major trials using **IIb/IIIa** inhibitors

Previous trials of IIb/IIIa inhibitors have also measured the occurrence of TIMI-class bleeding, and the available results for two of them are summarized below.

A. Reopro ***(abciximab)***

The first table below shows the incidence of major and minor bleeding from the three efficacy trials performed as part of the Reopro NDA.

Table 8.1.7.1e.3.1 Incidence of bleeding within 30 days according to TIMI criteria in the EPIC, EPILOG, and CAPTURE trials[a].

| | Abciximab | Abciximab bolus +low-dose Heparin | Placebo |
|---|---|---|---|
| **EPIC Trial[c]** | **n=708** | | **n=696** |
| TIM1 Major bleeds | 99 (14%) | | 46 (7.0%) |
| TIMI Minor bleeds | N/A | | N/A |
| Requiring Transfusion | N/A | | N/A |
| **CAPTURE Trial[b,c]** | **n=630** | | **n=635** |
| TIMI Major bleeds | N/A | | N/A |
| TIMI Minor bleeds | N/A | | N/A |
| Requiring Transfusion | N/A | | N/A |
| **EPILOG Trial** | **n=918** | **n=935** | **n=939** |
| TIMI Major bleeds | 32 (3.5%) | 19 (2.0%) | 29 (3.1%) |
| TIMI Minor bleeds | 37 (4.0%) | 68 (7.4%) | 35 (3.7%) |
| Requiring Transfusion (PRBCs) | 30 (3.3%) | 18 (1.9%) | 37 (3.9%) |

a. Data from Reopro package insert.

b. Data from (2).

c. Bleeding categorized per TIMI classification (10).

8.1.7.1e.3 Comparison of the incidence of major bleeding **in the major trials** using **IIb/IIIa** inhibitors **(cont)**

The next table shows the incidence of major and minor bleeding in the Reopro trials, excluding those subjects who underwent CABG.

Table 8.1.7.1e.3.2 Incidence of bleeding within 30 days according to TIMI criteria for those in the EPIC, EPILOG, and CAPTURE trials not associated with CABG[a].

| | Abciximab | Abciximab bolus +low-dose Heparin | Placebo |
|---|---|---|---|
| **EPIC Trial[c]** | **n=708** | | **n=696** |
| TIM1 Major bleeds | 75 (10.6%) | | 23 (3.3%) |
| TIM1 Minor bleeds | 119 (16.8%) | | 64 (9.4%) |
| Requiring Transfusion | 55 (7.8%) | | 14 (2.0%) |
| **CAPTURE Trial[b,c]** | **n=630** | | **n=635** |
| TIMI Major bleeds | 24 (3.8%) | | 12 (1.9%) |
| TIMI Minor bleeds | 30 (4.8%) | | 13 (2.0%) |
| Requiring Transfusion | 15 (2.4%) | | 9 (1.4%) |
| **EPILOG Trial[c]** | **n=918** | **n=935** | **n=939** |
| TIMI Major bleeds | 17 (1.9%) | 10 (1.1%) | 10 (1.1%) |
| TIMI Minor bleeds | 70 (7.6%) | 37 (4.0%) | 32 (3.4%) |
| Requiring Transfusion (PRBCs) | 7 (0.8%) | 6 (0.6%) | 10 (1.1%) |

a. Data from Reopro package insert.
b. Data from (2).
c. Bleeding categorized per TIMI classification (10).

***B. Integrilin (eptifibatide)***

Summaries of the bleeding events according to severity (TIM1 criteria) for the PURSUIT and IMPACT-II trials are shown below.

For the PURSUIT trial, which followed a protocol similar to the PRISM-PLUS and PRISM trials, the first table summarizes all bleeding. The second table summarizes the bleeding from those subjects who did not receive CABG by day 30 (84.6% of the subjects in the trial).

Table 8.1.7.1e.3.3 Incidence of bleeding within 30 days according to TIMI criteria in the PURSUIT trial[a].

| **TIMI Bleeding Status and need for transfusion** | **Eptifibatide (n=4679)** | **Placebo (n=4696)** |
|---|---|---|
| TIMI Major bleeds | 498 (10.8%) | 425 ( 9.3%) |
| TIMI Minor bleeds | 604 (13.1%) | 347 ( 7.6%) |
| Insignificant or None | 3502 (76.1%) | 3805 (83.1%) |
| **Requiring transfusion** | 550 (11.8%) | 438 ( 9.3%) |
| **Unresolved** | 75 (1.6%) | **119 (2.5%)** |

a. Data from NDA 20-718 and primary medical officer review (Dr. Isaac Hammond).
b. Transfusion with either packed RBCs or whole blood

Table 8.1.7.1 e.3.4 Incidence of bleeding within 30 days according to TIMI criteria for those subjects in the PURSUIT trial not associated with CABG".

| **TIM1 Bleeding Status and need for transfusion** | **Eptifibatide (n=4679)** | **Placebo (n=4696)** |
|---|---|---|
| TIMI Major bleeds | 121 (3.1%) | 50 (1.3%) |
| TIM1 Minor bleeds | 448 (11.5%) | 190 (4.9%) |
| Insignificant or None | 3337 (85.4%) | 3604 (93.8%) |
| **Requiring transfusion** | N/A | N/A |
| **Unresolved** | 67 (1.4%) | 110 (2.3%) |

a. Data from NDA 20-718 and primary medical officer review (Dr. Isaac Hammond).
b. Transfusion with either packed RBCs or whole blood

**8.1.7.1e.3** Comparison of the incidence of **major** bleeding in the major trials using **IIb/IIIa** inhibitors **(cont)**

For the IMPACT-II trial, which utilized a protocol similar to the RESTORE trial, only the overall incidence of major and minor bleeding is available to the reviewer.

Table 8.1.7.1e.3.5 Incidence of bleeding according to TIMI criteria in the IMPACT-II trial".

| **TIMI Bleeding Status and need for transfusion** | **Eptifibatide 135/0.5 (n=1249)** | **Eptifibatide 13510.75 (n=1245)** | **Placebo (n=1230)** |
|---|---|---|---|
| TIM1 Major bleeds | 55 (4.4%) | 58 (4.7%) | 55 (4.5%) |
| TIMI Minor bleeds | 146 **(11.7%)** | 177 (14.2%) | 115 (9.3%) |

a. Data from published paper and from Advisory Committee Briefing Document (128.98). Data shown excludes 147 subjects with insufficient data for analysis.

8.1.7.1e.3 Incidence of life-threatening bleeding in the combined tirofiban safety database

Three of the most serious bleeding events retroperitoneal, pericardial, and intracranial hemorrhage. The first table below shows the incidence of these events in the three Phase II-III trials for tirofiban. For details on the severity of the bleeding in each case, see the individual trial reviews.

Table 8.1.7.1e.2.3.1 Occurrence of life-threatening bleeding AEs in the phase II-III trials'.

| | **Tirofiban (N=2032)** | **Tirofiban+ Heparin (N=1953)** | **Heparin (N=3546)** |
|---|---|---|---|
| **PRISM-PLUS** | | | |
| Retroperitoneal bleeds | 2 | 0 | 1 |
| Intracranial bleeds | 0 | 0 | 0 |
| Cardiac tamponade | 1 | 2[b] | 0 |
| **PRISM** | | | |
| Retroperitoneal bleeds | 1 | 0 | 1 |
| Intracranial bleeds | 2 | 0 | 2 |
| Cardiac tamponade | 1 | 0 | 1 |
| **RESTORE** | | | |
| Retroperitoneal bleeds | 0 | 6 | 3 |
| Intracranial bleeds | 0 | 1 | 3 |
| Cardiac tamponade | 0 | 2[d] | 1 |
| ***Overall*** | | | |
| Retroperitoneal bleeds | 3 (0.15%) | 7 (0.46%)[c] | 5 (0.14%) |
| Intracranial bleeds | 2 (0.098%) | 1 (0.05%) | 5 (0.14%) |
| Cardiac tamponade | 1 (0.05%) | 4 (0.20%) | 2 (0.06%) |

a Data from individual trial reports and validated with the sponsor.
b. Both IC bleeds occurred at day 11 and day 14 (post-study drug).
c. One retroperitoneal bleed took place in protocol 007 (AN 241), occurring on day 1 of study drug administration.

For comparison, in the Reopro database, the incidence of intracranial hemorrhage was 3/2225 (0.13%) for placebo and 6/3 112 (0.19%) for subjects receiving Reopro.

8.1.7.1e.3 **Incidence of life-threatening bleeding in the combined tirofiban safety database (cont)**

At the reviewer's request, the sponsor supplied the following information about the subjects who had intracranial, retroperitoneal, and pericardial bleeding in the 'phase III trials. Most of the AEs occurred well-after the completion of study drug infusion. Those AEs which were temporally closely associated with study drug are shown in bold letters for emphasis. In the RESTORE trial, tirofiban +heparin was temporally associated with 5 retroperitoneal bleeds (5/1071=0.47%), compared with 2 in the heparin group (2/1070 = 0.19%). More intracranial bleeds were temporally associated with the heparin-alone treatment group.

Tab 8.1.7.1e.2.3.2 Subject listing of retroperitoneal bleeding in the phase I III trials*.

| Study and Subject # | Treatment Group | Time of Onset |
|---|---|---|
| PRISM-PLUS | | |
| AN 6074 | **Tirofiban** | **Day 4** |
| AN 6318 | Tirofiban | Day 11 |
| **AN 6676** | Heparin | **Day** 18 |
| PRISM | | |
| **AN 2325** | Tirofiban | **Day 8** |
| **AN 4446** | Heparin | Day 9 |
| RESTORE | | |
| **AN 1809** | **Tirofiban + Heparin** | **Day** 1 |
| **AN 1386** | Tirofiban + Heparin | Day 15 |
| **AN2003** | **Tirofiban + Heparin** | **Day 2** |
| **AN 1777** | **Tirofiban + Heparin** | **Day 2** |
| **AN 2516** | **Tirofiban + Heparin** | **Day 3[b]** |
| **AN 2566** | **Tirofiban + Heparin** | **Day 2[b]** |
| **AN 1445** | **Heparin** | **Day 1** |
| **AN 1531** | Heparin | Day 7 |
| **AN 5045** | **Heparin** | **Da) 2** |
| **Protocol 007** | | |
| **AN 241** | **Tirofiban +Heparin** | **Day 1** |

a. Di from sponsor, not independently confirmed by CRF examination by FDA.
b. AE felt to be *possibly* drug-related by principle investigator of trial

Table 8.1.7.1 e.2.3.3 Subject listing of intracranial bleeding in the phase II-III trials".

| Study and Subject # | Treatment Group | Time of Onset/ Notes |
|---|---|---|
| PRISM | | |
| **AN 2131** | **Tirofiban** | **Day 3, "A small hemorrhage that may have been caused by a fall 1 week prior to the patient's admission"** |
| **AN 1053** | Tirofiban | Day 25, "Readmitted ependymoma, necrosis & hemorrhage" |
| **AN 3280** | Heparin | Day 16 |
| **AN 1320** | Heparin | **Day 2** |
| RESTORE | | |
| **AN 1286** | Tirofiban + Heparin | Day 2, Post-Procedure AE, "patient was also receiving heparin, aspirin, coumadin and ticlopidine" |
| **AN 2077** | **Heparin** | **Day 1** |
| **AN 1954** | Heparin | Day 24 |
| **AN 3775** | Heparin | **Day 3** |

a. Data from sponsor, not independently confirmed by CRF examination by FDA.

Table 8.1.7.1e.2.3.4 Subject listing of pericardial bleeding in the phase II-III trials[a].

| Study and Subject # | Treatment Group | Time of Onset/ Notes |
|---|---|---|
| ***PRISM-PLUS*** | | |
| **AN 6141** | Tirofiban | Day 14 |
| **AN 1686** | Tirofiban + Heparin | Day 14 |
| **AN 1567** | Tirofiban + Heparin | Day 11 |
| ***PRISM*** | | |
| **AN 5597** | **Tirofiban** | **Day 2, Post-CABG** |
| **AN 2467** | Heparin | Day 15 |
| ***RESTORE*** | | |
| **AN 1848** | **Tirofiban + Heparin** | **Day 1, Post-Infarction Pericarditis[b]** |
| **AN 1809** | **Tirofiban + Heparin** | **Onset Day 1, LAD perforation** |
| **AN 1158** | **Heparin** | **Day 1, LAD perforation** |

a. Data from sponsor, not independently confirmed by CRF examination by FDA.
b. AE felt to be possibly drug-related by principle investigator of trial.

8.1.7.2 Thrombocytopenia

Thrombocytopenia in *the phase* II-III dafabase

Table 8.1.7.1.1 below shows the overall incidence of decreased platelet counts in the Phase II and Phase III trials. Overall, the rates of thrombocytopenia (<90,000/mm$^3$) was 1.5% in the tirofiban + heparin group, and 1.2% in the tirofiban alone group, versus 0.6% for all heparin subjects. Severe thrombocytopenia (<50,000/mm$^3$) was rare in the database, but occurred with a higher incidence in the tirofiban-treated subjects. Platelet transfusions were not more common in the tirofiban +heparin group when compared with heparin/ procedures. Subjects who received tirofiban alone, however, had a higher incidence of thrombocytopenia than their paired heparin group. The mechanism(s) for thrombocytopenia associated with the use of tirofiban are unknown at this time. Drug-dependent anti-platelet antibodies are a well-known cause for thrombocytopenia induced by a variety of drugs, but have not been investigated for this product.

Table 8.1.7.2.1 Incidence of decreased platelet counts and platelet transfusion in the tirofiban phase II-III database.

| | Tirofiban + Heparin n=1953 | Heparin/ Procedures n=1887 | Tirofiban n=2032 | Heparin/ No Procedures n=1659 | Total Heparin Alone n=3546 |
|---|---|---|---|---|---|
| Platelet count decrease to <90,000/mm$^3$ | 29 (1.5%) | 15 (0.8%) | 24 (1.2%) | 8 (0.5%) | 23 (0.6%) |
| Platelet count decrease to <50,000/mm$^3$ | 6 (0.3%) | 3 (0.2%) | 7 (0.3%) | 2 (0.1%) | 5 (0.1%) |
| Platelet count decrease to<20,000/mm$^3$ | 1 (0.1%) | 1 (0.1%) | 4 (0.2%) | 1 (0.1%) | 2(<0.1%) |
| Received platelet transfusion | 6 (0.3%) | 6 (0.3%) | 13 (0.6%) | 4 (0.2%) | 10 (0.3%) |

In each tirofiban patient, the thrombocytopenia resolved after study drug discontinuation. The 5 tirofiban subjects with platelet count decreases to <20,000/mm$^3$ are summarized below.

Narratives for subjects who developed marked thrombocytopenia.

1. AN 6953/PRISM-PLUS This 64-year-old male with a pre-study platelet count of 1 62,000/mm$^3$ suddenly began to have severe chills and generalized shaking 55 minutes after initiation of study drugs (tirofiban plus heparin), so study drugs were stopped. His rectal temperature at the onset of the chills was 37.7°C. Blood work obtained 1 hour and 45 minutes after start of study drugs showed a dramatic drop of platelet counts to 3000/mm 3 . His rectal temperature rose to 38.8°C, and a repeat platelet count 30 minutes later was at 5000/mm$^3$. Other than mild arm bruising, the patient had no clinical evidence of any overt bleeding and was feeling fine. The next day (Day 2) his platelet counts were 6000/mm$^3$ and 26,000/mm$^3$, and continued to rise daily. The platelet count returned to pre-drug values by Day 7 (Day 3: 42,000/mm$^3$, Day 6: 133,000/mm$^3$, Day 7: 173,000/mm$^3$, Day 8: 191,000/mm$^3$) . The investigator considered the thrombocytopenia to be drug related and potentially life-threatening.

2. AN 49191 PRISM: This 43-year-old male experienced a platelet count of 6000/mm$^3$ 24 hours after initiation of tirofiban, without concomitant heparin, down from a baseline of 18 1,000/mm$^3$. He developed epistaxis associated with the thrombocytopenia. His platelet count recovered to 90,000/mm$^3$ by Day 6, after discontinuation of the study drug. The thrombocytopenia and epistaxis were considered by the investigator to be probably drug related.

3. AN 7520/ PRISM: This 64-year-old female experienced a platelet count of 8000/mm$^3$ approximately 23.5 hours after discontinuation of tirofiban, which had been infused for 47.5 hours, without concomitant heparin. The patient's baseline platelet count was 167,000 mm$^3$. Just prior to the tirofiban infusion, the patient's platelet count was 202,000/mm$^3$. The patient had also received abciximab, which the investigator considered to be the precipitating cause of the thrombocytopenia. She had no bleeding complications associated with the thrombocytopenia. The investigator reported the duration of the thrombocytopenia to be 13.5 hours. The thrombocytopenia was considered by the investigator to be probably not study drug related.

4. AN 3605/ PRISM: This 74-year-old female experienced a platelet count of 16,000/mm$^3$ 49 hours after initiation of tirofiban, without concomitant heparin, down from a baseline of 305,000/mm$^3$. She had no bleeding complications associated with the thrombocytopenia. Her platelet count recovered to 85,000/mm$^3$ by Day 4, and was 376,000/mm$^3$ when rechecked on Day 44. The tbrombocytopenia was considered by the investigator to be defmitely drug related.

5. AN 1462/ PRISM: This 51-year-old female experienced a platelet count of 19,000/mm$^3$ 17.5 hours after initiation of tirofiban, without concomitant heparin, down from a baseline of 172,000/mm$^3$. She experienced epistaxis which was considered by the investigator to be definitely not drug related. Her platelet count recovered to 109,000/mm$^3$ by Day 5. The thrombocytopenia was considered by the investigator to be probably drug related.

8.1.7.2 Thrombocytopenia (cont)

Incidence of thrombocytopenia with other *IIb/IIIa* inhibitors

A. Reopro (abciximab)

In the trials reported below, thrombocytopenia was more common in the Abciximab treatment groups for all three trials. More subjects also received platelet transfusions.

Table 8.1.7.2.2 Thrombocytopenia and platelet transfusions in the EPIC, EPILOG, and CAPTURE trials".

| | Placebo | Abciximab n=708 | Abciximab bolus +low-dose Heparin |
|---|---|---|---|
| **EPIC Trial** | n=696 | n=708 | |
| Number of subjects with platelet counts 400,000 cells/µl | 3.4% | 5.2% | |
| Number of subjects with platelet counts -30,000 cells/µl | 0.7% | 1.6% | |
| Requiring Platelet Transfusion | 2.6% | 5.5% | |
| **CAPTURE Trial** | n=635 | n=630 | |
| Number of subjects with platelet counts <100,000 cells/µl | 1.3% | 5.6% | |
| Number of subjects with platelet counts <50,000 cells/µl | 0.3% | 1.7% | |
| Requiring Platelet Transfusion | 0.3% | 2.1% | |
| **EPILOG Trial** | n=939 | n=918 | n=935 |
| Number of subjects with platelet counts 400,000 cells/µl | 1.5% | 2.6% | 2.5% |
| Number of subjects with platelet counts <50,000 cells/µl | 0.4% | 0.9% | 0.4% |
| Requiring Platelet Transfusion | 1.1% | 1.6% | 0.9% |

a. Data from Reopro package insert.

B. **Integrilin (eptifibatide)**

The incidence of thrombocytopenia was not different in the two study populations in the PURSUIT trial. A numerical excess of subjects had marked decreases in platelet number and/or required platelet transfusions in the eptifibatide group. No data is available on the incidence of thrombocytopenia in the IMPACT-II trial.

ble 8.1.7.2.3 Incidence of low platelets counts post-baseline for subjects in th PURSUIT trial[a].

| Platelet Count | Placebo | Eptifibatide |
|---|---|---|
| <100,000/µL | 225/4587 (5%) | 226/4599 (5%) |
| ≥50% decrease from baseline | 231/4516 (5%) | 250/4544 (5%) |
| <50,000/µL | 19/4587 (<1%) | 26/4599 (1%) |
| <20,000/µL | 2/4587 (<1%) | 9/4599 (<1%) |
| **Subjects requiring platelet transfusion** | 104 ( 2.2%) | 122 ( 2.6%) |

Data from NDA 20-718 and primary medical officer review (Dr. Isaac Hammond).

The incidence of thrombocytopenia in the IMPACT-II trial was reported not to differ among the treatment groups, but specific data are not available to this reviewer (see Medical Officer's review of NDA 20-718 dated 1.26.97, page 81).

8.1.7.3 Neutropenial Agranulocytosis

In the clopidogrel database, there was a significant association between Abciximab administration and neutropenia/ agranulocytosis. According to the proposed label, . . .'although the risk of myelotoxicity with clopidogrel thus appears to be low, this possibility should be considered when a patient receiving clopidogrel demonstrates fever or other signs of infection.' The number of subjects with significant decreases in neutrophil counts are shown below.

Table 8.1.7.3.1 Clinically significant decreases in neutrophil count in the CAPRIE study[a].

| Neutropenia/agranulocytosis | ASA n=9586 | Plavix n=9599 |
|---|---|---|
| Agranulocytosis | 0 | 2 |
| 0<Neutrophil # <450/mm$^3$ | 2 | 2 |
| 450 <Neutrophil # <1200/mm$^3$ | 20 | 22 |

a. Data from proposed Plavix label, submitted 11.3.97 to the Division of Cardio-Renal Drug Products and from NDA 20-839 Medical Review, page 31.

In the tirofiban safety database, no subjects developed agranulocytosis. The number of subjects who had marked decreases in neutrophil counts are shown below for each of the treatment groups. There was no difference in the incidence between groups.

Table 8.1.7.3.2 Number and percentage of subjects with markedly decreased WBC count in the phase II-III trials of tirofiban from NDA 20-912[a].

| | Tirofiban + Heparin | Heparin/ Procedures | Tirofiban | Heparin/ No Procedures | Total Heparin Alone |
|---|---|---|---|---|---|
| Hematology WBC count: value <4500/mm$^3$ | 68/1729 (3.9%) | 65 1758 (3.7%) | 76/1887 (4.0%) | 83/1558 (5.3%) | 148/3316 (4.5%) |

a. Data from NDA volume 1.37, Table D-70 and electronic datasets.

Per the sponsor, only one individual developed a WBC count ≤2000 /mm$^3$, and her narrative is included below.

1. AN 7521: The patient was a 71 year old female with a history of diabetes, myocardial infarction, hypertension; and previous angiography who was admitted for unstable angina, enrolled in the RESTORE trial, and received tirofiban +heparin. All of the reported WBC count values for this patient are shown below.

| Study Time | WBC # (/mm$^3$) |
|---|---|
| -6:50 | 7800 |
| 04:10 | 8600 |
| 23:59 | 8300 |
| 48:10[a] | 8700 |
| 72:38[a] | 1100 |

a Subject off-drug.

She did not have an SAE reported for this event, and did not have any other SAEs reported. Her baseline medications included captopril, metoprolol, aspirin, indomethacin, isosorbide, and amlodipine. Her concomitant medications included amlodipine, aspirin, bromazepam, metoprolol, and nitroglycerin. There is no further follow-up information available on the patient.

8.1.7.4 Abnormal Liver Function Tests (LFTs)

While the pharmacology of tirofiban suggests that it is minimally metabolized in humans (see section 4.0.2 Pre-clinical Pharmacokinetics), a standard analysis performed as part of a safety assessment is the effect of the drug on the liver. In this review, liver function test abnormalities and the incidence of severe liver injury will be summarized.

SAE related to abnormal liver functions

No SAE related to hepatic function occurred at 20.5% incidence in the phase II-III database (see Table 8.1.2.1 p. 197). In the entire dataset of SAEs, there were no cases of 'hepatitis,' jaundice,' or 'liver failure' (See NDA vol. 1.65, ref. 88, and from medical officer discussion with sponsor). In the heparin group, one individual was reported to have 'hepatic insufficiency' (and none in the tirofiban groups).

There were no discontinuations for abnormal LFTs or liver failure.

8.1.7.4 Abnormal Liver Function Tests **(LFTs) (cont)**

Laboratory **AEs** related to abnormal **LFTs**

In the adverse events related to lab abnormalities above, it was noted that there was an increased incidence of elevated AST (Aspartate transaminase =SGOT) in the tirofiban groups. The sponsor notes that AST is released following myocardial ischemia. To address the potential hepatotoxicity of tirofiban, the sponsor performed a series of analyses, focusing on abnormalities in the ALT (Alanine transaminase or SGPT). Included are the number of subjects with available data.

First, the incidence of LFTs outside the normal range was tabulated, and the results shown in the first table below. As can be seen, there was a slightly higher incidence of elevated AST in the tirofiban +heparin group (4.3%) vs. the paired heparin subjects (3.8%) and vs. the overall heparin alone group (2.6%). There was also a higher incidence of urinary bilirubin in the tirofiban groups. Alkaline phosphatase was also slightly increased in the tirofiban +heparin group vs. the heparin groups. Elevations in ALT occurred equally in all groups. The incidence of abnormal total bilirubin values was rare, but higher in the heparin groups.

Table 8.1.7.4.1 Incidence of labs outside the normal range in the phase II-III trials[a].

| | Tirofiban + Heparin | Heparin/ Procedures | Tirofiban | Heparin/ No Procedures | Total Heparin Alone |
|---|---|---|---|---|---|
| **Serum Chemistry** | | | | | |
| ALT increased | 63/1709 (3.7%) | 64/1647 (3.9%) | 17/1869 (0.9%) | 17/1529 (1.1%) | 81/3176 (2.6%) |
| AST increased | 78/1811 (4.3%) | 66/1752 (3.8%) | 18/1864 (1.0%) | 18/1527 (1.2%) | 84/3279 (2.6%) |
| Alk phos increased[c] | 7/1792 (0.4%) | 4/1730 (0.2%) | 4/1866 (0.2%) | 2/1524 (0.1%) | 6/3254 (0.18%) |
| Bilirubin increased | 2/1819 (0.1%) | 7/1749 (0.4%) | 1/1868 (0.1%) | 0/1530 (0.5%) | 7/3279 (0.2%) |
| Urinalysis | | | | | |
| Urine bilirubin increased | 6/645 (0.9%) | 3/659 (0.5%) | 8/1656 (0.5%) | 111383 (0.1%) | 4/2042 (0.2%) |

a. Data from NDA volume 1.2, Table C-39, volume 1.37, Table D-63, and electronic datasets.

b. Per protocol, platelet counts that decreased more than 1/3 from baseline were counted as an adverse event, whether or not the platelet count fell within the normal range. This row reflects the numbers of these events.

c. Alk phos = alkaline phosphatase

At the request of the medical officer, the incidence of these abnormalities was grouped according to height of the abnormality (a single value >2X, >3X or >5X above the upper limits of normal, regardless of when it was drawn). Appendix nine (section 2 1 .O) has a listing of subjects with abnormal LFTs, including those with extreme elevations.

Table 8.1.7.4.2 Incidence at least one elevated LFT above upper limits of normal in the phase II-III trials[a].

| Single abnormal LFT reading (n/N with available data (%)) | Tirofiban | Tirofiban +Heparin | Heparin/ |
|---|---|---|---|
| **ALT** | | | |
| >2X above upper limit of nl | 112/1605 (7.0%) | 53/1799 (2.9%) | 159/3116 (5.1%) |
| >3X above upper limit of nl | 37/1605 (2.3%) | 18/1799 (1.0%) | 13/3116 (0.4%) |
| >5X above upper limit of nl | 9/1605 (0.6%) | 3/1799 (0.2%) | 13/3116 (0.4%) |
| >10X above upper limit of nl | 2/1605 (0.12%) | 1/1605 (0.06%) | 5/3116 (0.16%) |
| **Alkaline Phosphatase** | | | |
| >2X above upper limit of nl | 6/1691 (0.4%) | 3/1706 (0.2%) | 16/3 196 (0.5%) |
| >3X above upper limit of nl | 2/1691 (0.1%) | 0/1796 (0%) | 1/3 196 (<0. 1%) |
| >5X above upper limit of nl | 0/1691 (0%) | 0/1796 (0%) | 113196 (<0.1%) |
| ***Bilirubin*** | | | |
| >2X above upper limit of nl | 17/1717 (1.0% | 10/1798 (0.6%) | 2513222 (0.8%) |
| >3X above upper limit of nl | 4/1717 (0.2%) | 1/1798 (0.1%) | 6/3222 (0.2%) |
| >5X above upper limit of nl | 2/1717 (0.1%) | 0/1798 (0%) | 113222 (<0.1%) |

a. Data per sponsor at request of medical officer.

8.1.7.4 Abnormal Liver **Function Tests (LFTs) (cont)**

The sponsor also analyzed the incidence of subjects who had a large change in ALT and bilirubin from baseline. The total number of subjects with elevations in ALT in the PRISM-PLUS, PRISM, and RESTORE trials were as follows: ≥2X above baseline measurement, 1102; ≥3X, 439; 25X. 122 subjects. The next two tables summarizes these subjects according to treatment group for ACT and bilirubin. For ALT, the highest incidence of marked abnormalities (>5X) occurred in the heparin groups.

ıble 8.1.7.4.3 Ranked incidence of elevated ALT above baseline in the pha: III trials".

| | **Tirofiban** **(n/N with available data (%)** | **Tirofiban +Heparin** **(n/N with available data (%)** | **Heparin/** (n/N with available **data (%)** |
|---|---|---|---|
| **PRISM-PLUS** | | | |
| >2X above upper limit of nl | 50/138 **(16.2%)** | 2701711 (38.0%) | 259/726 (35.7%) |
| >3X above upper limit of nl | 19/308 (6.2%) | 126/711 (17.7%) | 125/726 (I 7.2%) |
| >5X above upper limit of nl | 4/308 (1.3%) | 33/711 (4.6%) | 40/726 (5.5%) |
| **PRISM** | | | |
| >2X above upper limit of nl | 134/331 (10.1%) | | 243/1342 (18.%) |
| >3X above upper limit of nl | 45/133 1 (3.4%) | | 76/1342 (5.7%) |
| >5X above upper limit of nl | 1311331 (1.0%) | | 19 (1342 (1.4%) |
| **RESTORE** | | | |
| >2X above upper limit of nl | | 75/716 (10.4%) | 71/721 (9.8%) |
| >3X above upper limit of nl | | 26/716 (3.6%) | 22/72 (3.1%) |
| >5X above upper limit of nl | | 5/716 (0.7%) | 81721 (1.1%) |

Data per sponsor at request of medical officer.

Subjects in the tirofiban groups did have a numerically increased incidence of marked elevations in bilirubin, although the-numbers were small.

ıble 8.1.7.4.4 Incidence of marl d elevations in Bilirubin from baseline in the phase II-III trials".

| | **Tirofiban** **(n/N with available data (%)** | **Tirofiban +Heparin** **(n/N with available data (%)** | **Heparin/** **(n/N with** available data **(%)** |
|---|---|---|---|
| **PRISM-PLUS** | | | |
| >2X above upper limit of nl | 47/308 (15.2%) | 69/7 11 (9.7%) | 63/726 (8.7%) |
| >3X above upper limit of nl | 8/308 (2.6%) | 111711 (1.5%) | 20/726 (2.7%) |
| >5X above upper limit of nl | 2/308 (0.6%) | 2/711 (0.3%) | 3/726 (0.4%) |
| **PRISM** | | | |
| >2X above upper limit of nl | 87/1331 (6.5%) | | 97/1343 (7.1%) |
| >3X above upper limit of nl | 11/133 1 (0.8%) | | 1211343 (0.9%) |
| >5X above upper limit of nl | 2/133 1 (0.2%) | | 011343 (0%) |
| **RESTORE** | | | |
| >2X above upper limit of nl | | 29/828 (3.5%) | 31/830 (3.7%) |
| >3X above upper limit of nl | | 8/828 (0.9%) | 3/830 (0.4%) |
| >5X above upper limit of nl | | 3/828 (0.4%) | 2/830 (0.2%) |

Data per sponsor at request of medical officer.

8.1.7.4 Abnormal Liver **Function Tests (LFTs) (cont)**

The sponsor also defined a series of pre-defined critical limits, and collected data on the number of subjects with a value or a change in laboratory test outside of the limit. These subjects, along with the predefmed limits, are shown in the table below. Note that marked elevations in ALT were not more common in the tirofiban groups.

Table 8.1.7.4.5 Number and percentage of subjects with a value or a change in LFTs outside of defined limits in the phase II-III trials of tirofiban from NDA 20-912".

| | **Tirofiban + Heparin** | **Heparinl Procedures** | **Tirofiban** | **Heparinl No Procedures** | Total Heparin **Alone** |
|---|---|---|---|---|---|
| **Blood Chemistry** | | | | | |
| Serum alkaline phosphatase: **increase >30 U/dl** | 45/1462 (3.1%) | 5511492 (3.7%) | 30/1602 (1.9%) | 22/1329 (1.7%) | 77/2821 (2.7%) |
| ALT: increase >30 U/L | 180/1399 (12.9%) | 19411432 (13.5%) | 65/1639 (4.0%) | 69/1342 (5.1%) | 263/2774 (9.5%) |
| Bilirubin: increase >0.4 mg/dL | 114/1518 (7.5%) | 96 /1537 (6.2%) | 139/1639 (8.5%) | 87/1343 (6.5%) | 183/2880 (6.4%) |

a. Data from NDA volume 1.37, Table D-70 and electronic datasets. Numbers represent subjects with lab exceeding pre-set limits above normal.

Analysis of the association between marked (≥4-5X) elevations in **LFTs** and **clinical AEs**

At the reviewer's request, the sponsor also submitted information about the height of the abnormal LFTs, and their association with clinical AEs. The sponsor focused on ALT, alk phos and total bilirubin as markers of abnormal liver function. The listing in appendix nine (section 21.0) shows all subjects in the phase III trials who had at elevation in both ALT and bilirubin (with one ≥2X). The table also shows the occurrence of clinical AEs potentially related to hepatic injury (anorexia, hepatomegaly, cholelithiasis, cholecystitis, jaundice, pruritus, skin discoloration) or bleeding complications in these subjects with abnormal LFTs. The table below shows selected subjects from the appendix with marked elevations in one or more of their LFTs, and the clinical AEs associated with them. The lab values are shown as the fold-increase above upper limit of normal. Subjects in bold have extreme elevations in one or more of the lab values.

In the tirofiban +heparin group, one subject (AN 515 1) had a 15.5X increase over upper limits of normal for ALT, with no detected clinical AE referable to the liver. This subject also had a 2.0X increase in alkaline phosphatase, but a normal bilirubin. Another individual (AN 3731) had a 6.3X elevation in bilirubin, with no elevation in ALT or bilirubin. He also had no clinical AEs referable to the liver or bleeding AE.

In the heparin group, several individuals had marked elevations in ALT, up to 59.8X (AN 7066). This individual also had a bleeding AE. Another individual (AN 2975) had a 49.6X elevation of ALT above normal, along with a 2X elevation in bilirubin. Some of these elevations in ALT were associated with elevations in either Alkaline phosphatase or Bilirubin (see AN 1646 and 2975). It should be noted that extreme elevations in ALT/AST are included in the warnings as part of the heparin label. One individual, AN 5643, who received heparin alone, had a serious AE related to elevated ALT and AST, in association with increased WBC count. There were no reported long-term clinical. consequences. The CRFs for individual subjects have not yet been reviewed by the medical reviewer.

The tirofiban alone group had relatively few marked elevations in LFTs, but did have one individual with a 12.2X elevation in ALT associated with a 2.1X elevation in bilirubin, and another with a 9.5X elevation in ALT along with a 2-fold elevation in bilirubin. Neither subject had an AE referrable to the liver, or a bleeding AE.

Overall, there was no clear association between extreme elevations in LFTs and clinical AEs. The clinical significance of the two subjects with combined elevations of ALT and bilirubin in the tirofiban-alone group, and the one subject with a combined elevation of ALT and Alkaline phosphatase in the tirofiban +heparin group has yet to be determined. Several subjects in the heparin-alone group had combined elevations of ALT and bilirubin, or extreme (>20X) elevations of ALT.

## 8.1.7.4 Abnormal Liver Function Tests (LFTs)

Table 8.1.7.4.6 Listing of subjects in phase III trials with marked elevations of either ALT, alkaline phosphatase, or bilirubin, along with information about clinical AEs[a].

| Treatment Group & Subject # | ALT | Alk Phos | Bilirubin | Bleeding Comp[b] | Clinical AE |
|---|---|---|---|---|---|
| ***Tirofiban +Heparin*** Group | | | | | |
| **PRISM-PLUS** | | | | | |
| AN 1620 | **2.28** | **1.88** | **1.38** | TIMI Major | Pruritus (at hr 68) |
| AN 5355 | 4.97 | 1.74 | **0.25** | | |
| AN 6329 | **3.65** | **1.04** | **0.33** | **Y** | |
| **AN 6899** | **8.76** | 1.59 | **0.33** | | |
| **RESTORE** | | | | | |
| **AN 3015** | **0.52** | ND | **4** | | Pruritus |
| AN 2103 | **5.61** | **3.00** | 1 | | |
| **AN 2395** | **1.9** | **0.46** | **5.5** | | |
| **AN 5151** | **15.52** | **2.05** | **0.77** | | |
| **AN 3731** | 0.51 | **0.84** | **6.3** | | |
| Heparin Alone Group | | | | | |
| **PRISM-PLUS** | | | | | |
| AN 6651 | 1.68 | **0.50** | **2.38** | | Hepatic insufficiency, SAE |
| **AN 7066** | **59.77** | **0.52** | **1.24** | **Y** | |
| AN 1643 | 3.79 | 1.08 | **0.43** | | Cholelithiasis |
| AN 6888 | **5.13** | **0.55** | **1.81** | | |
| AN 7609 | **5.79** | **0.5** | **2.17** | | |
| **AN 7751** | **17.37** | **0.68** | **1.08** | | |
| **RESTORE** | | | | | |
| **AN 4833** | **10.28** | 1.69 | **3.04** | | |
| **AN 2390** | **8.14** | **0.38** | **0.666** | | |
| **AN 2975** | **41.7** | **0.991** | **2** | | |
| AN 6835 | **6.60** | **1.39** | **0.666** | | |
| **AN 3259** | **0.85** | **7.22** | **0.7** | **Y** | |
| **AN 1378** | **13.12** | **1.09** | **0.75** | | |
| **AN 1646** | **3.17** | **0.91** | **5.61** | | |
| **AN 1317** | **9.45** | **1.72** | **0.5** | | |
| **AN 1208** | **0.34** | **0.88** | **4.83** | | |
| **AN 5647** | **1.08** | **0.66** | **2.58** | | Pruritus at 35 hrs |
| ***Tirofiban*** Alone Group | | | | | |
| **PRISM-PLUS** | | | | | |
| **AN 4616** | **12.23** | 1.02 | **2.08** | | |
| AN 3106 | **4.53** | 1.93 | 0.81 | | |
| **AN 4974** | **29.69** | 1.99 | **0.42** | | |
| **AN 5705** | **2.53** | **2.59** | **0.66** | | |
| **AN 4678** | **9.53** | **0.8** | **2** | | |

a. Data from sponsor at request of medical reviewer. Data shown is selected from list of all subjects with ≥2X increase in ALT, Alk phos or bilirubin with either clinical AE or bleeding complication, submitted by sponsor.

b. Bleeding complications were defined as either a bleeding episode that was moderate, severe, or life-threatening, or a TIMI major-bleeding event. If the subject had both types of bleeding, the table entry is Y-TIMI Major.

8.1.7.4 Abnormal Liver Function Tests (LFTs) (cont)

Analysis of bleeding incidence, by treatment group, for subjects with 22X elevation of ALT, alk phos or bilirubin above upper limits of normal

Finally, the sponsor summarized the incidence of clinically significant bleeding in the subjects who had at least one lab value (ALT, bilirubin or alk phos) that was ≥2X upper limit of normal. There was no clear association between abnormal LFTs and clinically significant bleeding.

Table 8.1.7.4.7 Incidence of clinically significant bleeding events in the phase III trials for subjects with elevations in ALT, bilirubin or alk phos[a].

| Bleeding Category shown as n/N with available data (%) | Tirofiban | Tirofiban +Heparin | Heparin/ |
|---|---|---|---|
| TIMI Major bleeding | 2/72 (2.8%) | 1/143 (0.7%) | 3/215 (1.4%) |
| Moderate, severe or life-threatening bleeding | 5/72 (6.9%) | 13/143 (9.1%) | 19/215 (8.8%) |

a. Data per sponsor at request of medical officer. Data is for subjects with available data with a single lab value of ALT, bilirubin or alk phos ≥2X upper limits of normal.

8.1.8.1 Bleeding adverse event subgroup analyses from the PRISM, PRISM-PLUS, and RESTORE trials

The sponsor performed an analysis of the phase III data, examining the relationship between bleeding and three demographic factors: weight; age; and gender. Two comparisons were made: tirofiban vs. heparin (from the PRISM trial data), and tirofiban +heparin vs. heparin (from the tirofiban +heparin arm of PRISM-PLUS and RESTORE and the pooled heparin data from PRISM-PLUS and RESTORE). The tirofiban alone arm in the PRISM-PLUS trial was not separately analyzed (345 total subjects).

An analysis of the relationship between time of exposure to study drug and risk of bleeding for the phase II-III database, performed by the sponsor and received 3.30.98, will be submitted separately following review by the FDA. An analysis of the relationship between time of exposure to study drug and risk of bleeding for the PRISM-PLUS trial is included in section 8.1.7.1e.0 above.

No analysis of the relationship between the dose of tirofiban and risk of bleeding has been performed. Complicating such an analysis is that subjects were. dosed on a µg/kg basis (the relationship between body weight and the risk of bleeding was examined, and is found in in this section). These trials also had significant differances in the both the rates of cardiac procedures performed and in the dose of the bolus and infusion of tirofiban. Given that the risk of bleeding was increased following such procedures, this variability in study protocols complicates any analysis.

Interaction between tirotiban and weight with respect to bleeding risk

In preparing this analysis the sponsor used a regression model. In each of the individual studies, the sponsor analyzed the interaction of weight and study drugs relative to the incidence of major bleeding (protocol-defined), and the results of those analyses are shown below.

Table 8.1.8.1.1 (from table 6.2.2.12.3.6) Incidence of major bleeding grouped according to weight from the PRISM trial*.

| | Tirofiban | Heparin | 95% CI[b] |
|---|---|---|---|
| **Weight** | | | |
| Light (<75 kg) | 30/677 (4.4%) | 39/662 (5.9%) | 0.459, 1.223 |
| 75 to 85 kg | 19/455 (4.2%) | 281497 (5.6%) | 0.387, 1.285 |
| Heavy (>85 kg) | 12/482 (2.5%) | 24/455 (5.3%) | 0.224, 0.924 |

a Data from NDA 20-912, volume 1.48, ref 9, tables 21. Intent-to-treat population is used. NA= not applicable
b. CI per the sponsor based on logistic regression analysis.

Table 8.1.8.1.2 Incidence of major bleeding grouped according to weight from the PRISM-PLUS trial".

| | Tirofiban | Tirofiban +Heparin | Heparin , |
|---|---|---|---|
| **Weight** | | | |
| Light (<75 kg) | 14/174 (8.0%) | 19/365 (5.2%) | 14/373 (3.8%) |
| 75 to 85 kg | 4/93 (4.3%) | 8/219 (3.7%) | 6/209 |
| Heavy (>85 kg) | 0/77 (0%) ( | 4/189 (2.1%) | 4/215 (1.9%) |

a. Data from NDA 20-912, volume 1.42, ref 5, tables 41. Intent-to-treat population is used.

8.1.8.1 Bleeding adverse event subgroup analyses from PRISM, PRISM-PLUS, and RESTORE (cont)

Table 8.1.8.1.3 (from table 6.2.3.12.3.1) Incidence of major bleeding grouped according to weight in the RESTORE trial[a].

| | Tirofiban +Heparin n=1071 | Placebo +Heparin n=1070 | 95% CI[b] |
|---|---|---|---|
| Weight | | | |
| Light (<mean) | 64/594 (11.8%) | 67/543 (12.3%) | 0.595, 1.234 |
| Heavy (≥mean) | 46/477 (9.6%) | 63/527 (12.0%) | 0.523, 1.175 |

a. Data from NDA 20-912, volume 1.55, ref 11, tables 24. Intent-to-treat population is used. NA= not applicable
b. CI per the sponsor based on **logistic regression analysis.**

The sponsor then performed a logistic regression, with factors included as a continuous variables (except sex, which was an indicator variable). The overall results suggest that bleeding risk increases as weight decreases. The odds ratios in the table below indicate that, controlling for weight, tirofiban therapy was associated with excess bleeding relative to heparin; bleeding risk increased as weight decreased in all treatment groups (that is, the odds ratio adjusted for weight adjusted for tirofiban is <1.0).

Table 8.18.1.4 Interaction of tirofiban and weight with respect to bleeding AEs[a].

| | Odds ratio for effect of tirotiban (adjusted for weight) | Odds ratio for effect of weight (adjusted for tirofiban) | p-value for interaction between tirotiban and weight |
|---|---|---|---|
| Tirofiban vs. heparin, no procedures (PRISM) | 1.654 | 0.992/kg | 0.035 |
| Tirofiban vs. heparin, with procedures (PRISM-PLUS, RESTORE) | 1.919 | 0.986/kg | 0.82 |
| Tirofiban plus heparin vs. heparin, with procedures (PRISM-PLUS, RESTORE) | 1.664 | 0.989/kg | 0.14 |

a. Data from NDA volume 1.37, Table D-56 and reference 68. P value calculated by the sponsor.

Interaction between tirofiban and age with respect to bleeding risk

The sponsor also performed a similar analysis of the interaction of age and tirofiban with respect to bleeding. Controlling for age, tirofiban therapy was associated with increased risk of bleeding relative to heparin, which increased as age increased in all three groups examined. As the interaction between age and risk of bleeding was not significant in any of the groups, however, the sponsor concluded that the excess risk of bleeding in the tirofiban groups did not depend on the subject's age.

Table 8.1.8.1.5 Interaction of tirofiban and age with respect to bleeding AEs[a].

| | Odds ratio for effect of tirofiban (adjusted for weight) | Odds ratio for effect of weight (adjusted for tirofiban) | p-value for interaction between tirofiban and weight |
|---|---|---|---|
| Tirofiban vs. heparin, no procedures (PRISM) | 1.652 | 1.036/yr | 0.38 |
| Tirofiban vs. heparin, with procedures (PRISM-PLUS, RESTORE) | 1.943 | 1.030/yr | 0.56 |
| Tirofiban plus heparin vs. heparin, with procedures (PRISM-PLUS, RESTORE) | 1.707 | 1.029/yr | 0.94 |

a. Data from NDA volume 1.37, Table D-57 and reference 68. P value calculated by the sponsor.

**8.1.8.1 Bleeding adverse event subgroup analyses from PRISM, PRISM-PLUS,** and RESTORE **(cont)**

**Interaction between tirofiban and gender with respect to bleeding risk**

The sponsor also performed a similar analysis of the interaction of gender and tirofiban with respect to bleeding. In all cases; the bleeding risk was higher for the-women who received tirofiban. Again, due to lack of statistical significance for the interaction, the sponsor concluded that the excess risk of bleeding due to tirofiban was not due to the subject's **gender,** but suggested that tirotiban monotherapy in the context of procedures (second row of table) adds more to the risk of bleeding in women.

Table 8.1.8.1.6 Interaction of tirofiban and gender with respect to bleeding AEs[a].

| | **Odds** ratio for **effect of tirofiban (adjusted for gender)** | **Odds ratio for effect of weight (adjusted for tirofiban)** | **p-value for interaction between tirotiban and gender** |
|---|---|---|---|
| **Tirofiban vs. heparin, no procedures (PRISM )** | **1.629** | **1.797** (women relative to **men)** | 0.37 |
| **Tirotiban vs. heparin, with procedures ( PRISM-PLUS , RESTORE )** | **2.016** | **1.870** | 0.078 |
| **Tirofiban plus hepatin vs. hepariu, with, procedures ( PRISM-PLUS , RESTORE )** | 1.666 | 1.681 | **0.65.** |

a. Data from NDA volume 1.37, Table D-58 **end** reference 68. P value calculated by the sponsor.

**Interaction between tirofiban and creatinine clearance with respect to bleeding risk**

Finally, the sponsor examined the interaction of tirofiban and creatinine clearance with respect to bleeding risk. Again, controlling for creatinine clearance, tirofiban and tirofiban +heparin were associated with an increased risk of bleeding relative to heparin-alone. Additionally, bleeding risk increased as creatinine clearance decreased (second column). Again, due to lack of statistical significance for the interactions, the sponsor concluded that the excess risk of bleeding due to tirofiban was not due to the subject's creatinine clearance, but suggested that tirofiban monotherapy in the context of no procedures (first row of table) adds more to the risk of bleeding in subjects with low creatinine clearances. It should be remembered that there is a highly significant inverse relationship between creatinine clearance and plasma tirofiban clearance (for instance, see the PRISM trial, table 6.2.2.12.3.8).

Table 8.1.8.1.7 Interaction of tirofiban and creatinine clearance with respect to bleeding AEs[a].

| | **Odds ratio for effect of tirofiban (adjusted for CrCl)** | **Odds ratio for effect of CrCl (adjusted for *tirofiban*)** | **p-value for interaction between tirotiban and CrCl** |
|---|---|---|---|
| **Tirotiban vs. Heparin/ No procedures (PRISM )** | 1.690 | 0.987/ unit | 0.10 |
| **Tirotiban plus Heparin vs. Heparin/ Procedures ( PRISM-PLUS , RESTORE )** | 1.683 | 0.992/ unit | 0.55 |

a. Data from NDA volume 1.37, Table D-59 and reference 68. P value calculated by the sponsor.

8.1.8.2 Adverse events analyses by race

Tables 18.0.3 and 18.0.4, found in appendix six, show the percentage of clinical adverse experiences in subjects of various races occurring in ≥5.0% of subjects in any race subgroup/treatment group category and in at least 2 subjects in the subgroup. Due to the many comparisons, the table is broken into two parts: the first part displays the clinical AE profile for the tirofiban plus heparin and heparin/procedure groups only; the second part summarizes the clinical AEs in the tirofiban alone and heparin/no procedure groups. Overall, there were no clinically important differences across the different racial groups for subjects treated with tirofiban plus heparin, any apparent differences for specific AEs between the non-white groups should be interpreted with caution in light of the small patient numbers in some of the subgroups. There appears to be no clinically important increases in the rates in the non-white populations compared to the white population. For some bleeding adverse events, the rates of postoperative bleeding are lower in non-white populations. Compared to whites, blacks receiving tirofiban alone had a higher incidence of death.' However, blacks receiving tiroflban +heparin had a lower rate of death in the database than whites. The small total number of subjects makes it difficult to draw any firm conclusions. No race subgroup appeared to be at a consistently higher risk of developing a bleeding complication compared to whites.

For serious adverse events, the event rates for specific clinical events were low. Overall, there appeared to be no major differences in the rates of serious adverse events across racial groups in subjects treated with tirofiban (with or without heparin). Similarly, adverse events related to laboratory values were not more common in any of the race groups. Discussion of specific lab adverse events will appear in the appropriate section below.

Overall, given the small patient numbers in the various non-white subgroups, no clinically important differences were detected in subjects treated with tirotiban (with or without heparin) with respect to race.

8.1.8.3 Adverse events analyses by sex

Females comprised about 30% of the subjects in the Phase II and Phase III trials. Table 18.0.5, found in appendix six, shows the percentage of male vs. female subjects with clinical adverse events, occurring in ≥2.0% of the subjects in any gender subgroup/treatment group category. Within each of the treatment groups, females had slightly higher overall rates when compared with males for most adverse events. Women treated with tirofiban (with or without heparin) had a higher incidence (>2.0% higher in females than males) of hypotension, nausea, vomiting, back pain, headache, and urinary tract infections, than men treated with tirofiban. Females receiving tirofiban plus heparin also had a higher (22% compared to men) incidence of edema/swelling, vasovagal reactions, infused vein complications and leg pain.

In general, bleeding complications occurred more frequently in women compared to men. In particular, females receiving combination therapy had more postoperative bleeding, hematoma, hemorrhage, intravenous site hemorrhage, epistaxis, and ecchymosis compared to males and their female counterparts in the heparin/procedure group. However, these bleeding events were also increased in women within the heparin/ procedures group compared to men in this group.

Females also had a higher incidence of serious AEs than males; however, in general, there were no clinically significant between-treatment- group differences in the incidence rates. Similarly, no gender differences in the incidence of laboratory adverse events were noted that occurred at a different frequency in the tirofiban versus the non-tirofiban groups. Discussion of specific lab adverse events will appear in the appropriate section below.

Based on these findings, the sponsor concluded that, with the exception of vasovagal reactions in women receiving tirofiban plus heparin, there was no effect of tirofiban, with or without heparin, on the incidence of nonbleeding adverse experiences in women with respect to their heparin controls. There were more bleeding complications in women treated with tirofiban than men, but this was also true in the heparin-treated women. In section 8.1.8.1 above, data was presented which suggested a possible increased risk of bleeding for women who receive tirofiban, compared with men who receive tirofiban.

8.1.8.4 Adverse events analysis by age

The elderly patient population (≥65 years) comprised 42.8% of the subjects in the phase II-III trials. Table 18.0.6, found in appendix six, shows the percentage of subjects with clinical adverse experiences under the age of 65 years compared to subjects 65 years and older, occurring in 12.0% of subjects in any of the age subgroups/treatment group categories. Across all treatment groups (with and without tirofiban), there was a slightly higher incidence of overall clinical adverse events in the subjects ≥65 years of age compared to subjects <65 years of age.

Regarding non-bleeding AEs, the incidences of death, unstable angina, heart failure, cardiogenic shock, pulmonary edema, constipation, neurological disorders (agitation, confusion, nervousness, and somnolence), and ‘urogenital disorders (urinary tract infections) were higher in the ≥65 population than the <65 population across all treatment groups. Overall, the rates were generally comparable between the tirofiban groups and the corresponding heparin treatment-group comparators. In addition, subjects 265 years of age receiving tirofiban plus heparin had more (22% absolute difference in rates) nausea and vomiting than subjects <65 years of age; the rates, however, were comparable to the heparin/procedures group. Only constipation was increased in the older population receiving tirofiban alone compared with the *younger* population; this finding was also higher than the heparin/no procedures group.

Regarding bleeding AEs, events such as postoperative bleeding, hematoma, hemorrhage, hemorrhage IV site, epistaxis, ecchymosis, and hematuria were uniformly higher in subjects 265 than those <65 treated with tirofiban (with or without heparin). While this was also generally true of the corresponding heparin groups, note the pronounced *increase* in both hemorrhage and IV site hemorrhage in 265 year olds receiving tirofiban.

Regarding serious adverse events (SAEs), individuals 265 had a higher overall incidence of SAEs, as well as a higher incidence of certain SAEs, across all treatment groups. These are shown below.

8.1.8.4 Adverse events analysis by age (cont)

Table 8.1.8.4.1 Serious adverse events in the phase II-III database separated by age of subject[a].

| | Tirofiban + Heparin | | Heparin/ Procedures | | Tirofiban | | Heparin/ No Procedures | |
|---|---|---|---|---|---|---|---|---|
| | N=1174 | N=779 | N=1122 | N=765 | N=1093 | N=939 | N=920 | N=739 |
| | <65 | ≥65 | <65 | ≥65 | <65 | ≥65 | <65 | ≥65 |
| | % | % | % | % | % | % | % | % |
| **Percent of subjects with serious clinical AE** | 15.8 | 26.1 | 15.3 | 23.5 | 14.6 | 23.0 | 13.9 | 22.7 |
| **Body as a Whole/Site Unspecified** | 6.5 | 10.3 | 6.7 | 10.2 | 4.8 | 8.3 | 5.8 | 9.9 |
| Death | 0.3 | 4.5 | 1.0 | 4.7 | 1.3 | 5.0 | 2.0 | 6.0 |
| Cardiovascular System | 9.1 | 15.9 | 8.3 | 15.3 | 9.1 | 15.1 | 7.6 | 14.6 |
| Angina, unstable | 1.2 | 1.7 | 0.8 | 1.6 | 3.2 | 3.8 | 2.6 | 4.5 |
| Bleeding, postoperative | 0.6 | 1.0 | 0.5 | 1.2 | 0.3 | 1.1 | 0.3 | 0.3 |
| Shock, cardiogenic | 0.5 | 1.8 | 0.4 | 1.4 | 0.7 | 2.1 | 0.7 | 1.6 |

a. Data from NDA volume 1.37, table D-73.

In summary, the clinical adverse experience profile of tirofiban, with or without heparin, in subjects ≥65 years of age was similar to the respective heparin control groups and did not result in any untoward or unexpected safety concerns with respect to nonbleeding adverse experiences. Bleeding was more common in subjects 265 than in subjects <65 treated with tirofiban (with or without heparin), but this was also true of subjects <65 receiving heparin.

8.1.8.5 Adverse events analysis in subjects with renal and/or hepatic disease

Renal Disease

The NDA database is extremely limited with regard to information about subjects with renal insufficiency. This derives from the exclusion criteria for the three phase III trials, which excluded all subjects with elevated serum creatinines (12.0 mg/dl in the PRISM-PLUS and PRISM trials, ≥2.0 mg/dl in the RESTORE trial).

The effects of renal function on the pharmacokinetics of tirofiban were examined in protocol #014 (reviewed by Dr. Pelayo). They were also examined in the PRISM trial, using a subset of 762 subjects with available pharmacokinetic data. In that study, there was a significant relationship between the calculated creatinine clearance and the plasma tirofiban clearance, such that subjects with less than 30 ml/min of creatinine clearance had <50% of the normal tirofiban plasma clearance rate (p value for ANOVA relating creatinine clearance to tirofiban clearance ~0.001). Only 12 subjects had calculated creatinine clearances <30 ml/min in the PRISM database, limiting the strength of this inference.

Table 8.1.8.5.1 (from table 6.2.2.12.3.8) Tirofiban clearance during PRISM according to calculated creatinine clearance'.

| | <30 ml/min n=12 | 30-60 ml/min n=246 | 61-74 ml/min n=193 | ≥75 ml/min n=299 |
|---|---|---|---|---|
| Cl, (ml/min) | 94.98±42.1 | 146.4±67 | 174.99±84.7 | 207.31±86.5 |
| Cl, (ml/min) expressed as % of 275 ml/min $Cl_s$ | 45.8% | 70.5% | 84.5% | -- |

a. Data from NDA volume 1.48, ref. 9, table 16, and calculated by medical reviewer.

As discussed above, subjects with impaired renal function who received tirofiban +heparin were at non-significantly increased risk of bleeding when compared with heparin alone (see table 8.1.8.1.7, p. 239).

Hepatic disease

The effects of hepatic function on the pharmacokinetics of tirofiban were examined in protocol 009 (reviewed by Dr. Pellayo). No evaluation of the effect of hepatic disease on AEs in the tirofiban database was performed. An assessment of the relationship between abnormal LFTs and clinical AEs, including bleeding, was performed in section 8.1.7.4.

8.1.8.6 Adverse events analysis in subjects with hypertension

Adverse event profile for subjects with and without hypertension

Hypertensives accounted for about 55% of the subjects entered into the Phase II-III trials. Table 18.0.7, found in appendix-six, shows the percentage of subjects with clinical adverse experiences in subjects with a history of hypertension compared to those without a history of hypertension. Overall, in subjects receiving tirofiban (with or without heparin), the rates of clinical adverse experiences were similar between hypertensive and non-hypertensive subjects. For epistaxis and hematuria, there were slight increases in bleeding adverse experiences in the hypertensive population receiving tirofiban (with or without heparin). Nausea was increased (≥2% absolute difference in rates) in the tirofiban plus heparin hypertensives compared to non-hypertensives; the rate of nausea in that group, however, was less than the heparin/procedures control group.

Serious adverse event profile for subjects with and without hypertension

There was no significant differences in the overall incidence of SAEs between the hypertensive and non-hypertensive subjects (see NDA volume 1.37, table D-106 for details).

Laboratory adverse event profile for subjects with and without hypertension

There were no clinically relevant differences in the incidence of AEs related to serum chemistries or hematology for subjects with and without hypertension. There was, however, an increased incidence of hematuria and fecal occult blood in the hypertensive individuals who received tirofiban. There was also no differences in the incidence of serious lab AEs between the two groups (see NDA volumes 1.37, Tables D-107 and D-108 for details).

Table 8.1.8.6.1 Selected lab AEs for subjects grouped according to presence or absence of HTN[a].

| | Tirofiban | | Tirofiban +Heparin | | Heparin | |
|---|---|---|---|---|---|---|
| | HTN | Non-HTN | HTN | Non-HTN | HTN | Non-HTN |
| | N=1082 | N=950 | N=1068 | N=885 | N=1965 | N=1581 |
| **Urinalysis** Increased urine blood | 9.9% | 9.8% | 11.8% | 9.3% | 7.3 | 6.6 |
| **Fecal Occult Blood** | 10.8 | 8.4 | 20.0 | 16.0 | 7.9 | 6.4 |

8.1.8.7 Adverse events analysis in subjects with hypercholesterolemia

Adverse event profile for subjects with and without hypercholesterolemia

Hypercholesterolemics accounted for about 48% of the subjects entered into the Phase II and III trials. Table 18.0.8, found in appendix six, shows the percentages of clinical adverse experiences in subjects with hypercholesterolemia compared to those without hypercholesterolemia, occurring in 22.0% of the subjects in either subgroup/treatment group category. There were no major differences in the overall incidence rates of clinical adverse events between hypercholesterolemics and non-hypercholesterolemics receiving tirofiban (with or without heparin). In general, hypercholesterolemics receiving tirofiban plus heparin appeared to report more (≥2% absolute difference in event rates) pain (pelvic or back) than non-hypercholesterolemics; however, there were no major differences in the rates of these adverse experiences compared to hypercholesterolemics in the heparin/procedures group.

With regard to bleeding AEs, postoperative bleeding and epistaxis appeared to be somewhat higher in hypercholesterolemics receiving tirofiban plus heparin. Hemorrhage and IV site hemorrhage also appear to be more common in the diabetics who receive tirofiban.

Serious adverse event profile for subjects with and without hypercholesterolemia

There were no clinically important differences in the incidence rates of serious clinical adverse events between hypercholesterolemics and non-hypercholesterolemics (see NDA volume 1.37, table D-l 14).

8.1.8.7 Adverse events analysis in subjects with hypercholesterolemia (cont)

Laboratory adverse event profile for subjects with and without hypercholesterolemia

The only significant difference between the normo- and hyper-cholesterolemic subjects was an increase in the incidence of fecal occult blood (see NDA volume 1.37 table D- 115).

Table 8.1.8.7.1 Selected laboratory AEs in the phase II-III database separated by presence or absence of hypercholesterolemia[a,b].

| Selected lab AEs | Tirofiban | | Tirofiban +Heparin | | Heparin | |
|---|---|---|---|---|---|---|
| | Elevated Chol | Normal Chol | Elevated Chol | Normal Chol | Elevated Chol | Normal Chol |
| | n=955 | n=1077 | n=983 | n=970 | n=1710 | n=1836 |
| **Fecal occult blood** | 11.5% | 8.4% | 20.3% | 16.0% | 6.6% | 7.9% |

Serious laboratory adverse event profile for subjects with and without hypercholesterolemia

There was no significant difference in the incidence of serious lab AEs between hypercholesterolemics and non-hypercholesterolemics (see NDA volume 1.37, table D-l 16 for details).

8.1.8.8 Adverse events analysis in subjects with diabetes

Adverse event profile for subjects with and without diabetes

Diabetics accounted for about 2 1% of the subjects entered into the Phase II and III trials. Table 18.0.9, found in appendix six, shows the percentage of clinical AEs in subjects with diabetes compared to those without diabetes, occurring in 22.0% of the subjects in either subgroup/treatment group category. Diabetics treated with tirofiban plus heparin experienced more (≥2% absolute difference in events) chest pain and nervousness than non-diabetics; nervousness was also higher than in diabetics in the heparinlprocedures group, but this finding was not evident in the tirofiban-alone subjects and is unlikely to be of any major clinical importance. There was also a higher incidence of deaths in the diabetics in all groups.

With regard to bleeding AEs, epistaxis and hematuria were in the diabetic population treated with tirofiban (with or without heparin). Note that the diabetics had a higher incidence of death in both the tirofiban +heparin and the heparin/ procedures groups (increased equally in both groups).

Serious adverse event profile for subjects with and without diabetes

There was no clinically significant differences in the incidence of serious adverse events between the diabetic and non-diabetic subjects (see NDA volume 1.37, table 110 for details).

Laboratory adverse event profile for subjects with and without diabetes

There was no clinically significant differences in the incidence of laboratory-related AEs between the diabetic and non-diabetic subjects (see NDA volume 1.37, table 111 for details).

Serious laboratory adverse event profile for subjects with and without diabetes

There was no clinically significant differences in the incidence of serious laboratory-related AEs between the diabetic and non-diabetic subjects (see NDA volume 1.37, table 112 for details).

8.1.8.9 Adverse events analysis in according to duration of study drug administration

Duration of Exposure-related AEs

No information is available to this reviewer at this time concerning a possible interaction between duration of exposure to tirofiban and clinical AEs.

**8.1.8.10 Adverse events analysis for drug-drug interactions**

In the following section, the AEs occurring to subjects taking specific medications are compared with the AEs of the larger phase III population: thrombolytics (ticlid, war-farm, low-molecular weight heparin); cardiovascular drugs (calcium channel blockers, nitrates, &blockers); and non-steroidal anti-inflammatory drugs (NSAIDs). To compare the incidences of AEs with those of the overall subject population, see tables 8.1.3.1 and 8.1.3.2, p. 199.

Given the small number of subjects who took some of the medications, the sponsor reported only AEs which occurred ≥5.0% of any group. As was done for the previous AEs, the heparin group is subdivided into those with and without procedures. Data for the total heparin group is also show. No tabulation of the serious AEs and the lab AEs was performed by the sponsor, given the infrequency of these events in the subject subsets examined in this section.

I. Subjects taking antiplatelet/anticoagulant therapies, not including ASA and heparin

The first table shows the extent of the use of these compounds in the combined safety database.

Table 8.1.8.10.1 Number and % of subjects receiving antiplatelet/anticoagulant therapies other than ASA or heparin in the phase II-III database".

| Anticoagulant/antiplatelet drug | Tirofiban + Heparin n=1953 | Heparinl Procedures n=1887 | Tirofiban n=2032 | Heparinl No Procedures n=1659 |
|---|---|---|---|---|
| Ticlopidine | 153 (7.8%) | 134 (7.1%) | 56 (2.8%) | 34 (2.0%) |
| Warfarin | 196 (10.0%) | 207 (11.0%)~ | 32 (1.6%) | 38 (2.3%) |
| Low-molecular weight heparin | 29 (1.5%) | 26 (1.4%) | 28 (1.4%) | 28 (1.7%) |
| Thrombolytics | 23 (1.2%) | 29 (1.5%) | 17 (0.8%) | 11 (0.7%) |

a. Data from NDA volume 1.37, table D-86.

AEs in subjects taking Ticlopidine

Table 18.0.10, found in appendix six, shows the incidence of clinical AEs in subjects who received ticlid during the phase II-III trials. These event rates are to be compared with those of the overall subject population, which are summarized in tables 8.1.4.1 and 8.1.4.2 above. In general, while the rates of AEs were higher in the subjects who received tirofiban, when compared with the respective incidence rates for the overall population, no large differences were detected.

Similarly, the incidence of lab AEs was not significantly increased in subjects who took both tirofiban and ticlid. The heparin groups are combined due to the small number of events. There was a higher incidence of blood in the urine in both the tirofiban and the tirofiban +heparin groups compared with heparin. There was also a ≥3X increase in the incidence of fecal occult blood in the tirofiban +heparin group compared with heparin.

Table 8.1.8 3.2 Percentage of subjects receiving ticlopidine with lab AEs in the phase II-III database[a,b].

| | Tirofiban n=56 | Tirofiban + Heparin n=153 | Heparin n=168 |
|---|---|---|---|
| **Hematology** | 1.8% | 9.2% | 4.2% |
| Hematocrit decreased | 1.8% | 0.7% | 0.0% |
| Hemoglobin decreased | 1.8% | 1.3% | 0.6% |
| Lymphocytes decreased | 0.0% | 1.5% | 0.7% |
| Platelet count decreased | 0.0% | 1.3% | 1.2% |
| WBC count increased | 0.0% | 3.4% | 2.5% |
| **Chemistry** | 3.6% | 9.3% | 10.2% |
| ALTincreased | 1.9% | 2.3% | 3.6% |
| AST increased | 1.9% | 2.3% | 2.8% |
| Serum creatinine increased | 0.0% | 0.7% | 1.3% |
| Serum magnesium decreased | 0.0% | 0.0% | 1.4% |
| Serum potassium decreased | 0.0% | 1.4% | 2.5% |
| **Urinalysis** | 13.0% | 16.1% | 17.8% |
| Urine blood increased | 13.0% | 12.1% | 5.0% |
| Urine glucose increased | 0.0% | 0.0% | 1.5% |
| Urine protein increased | 0.0% | 0.9% | 1.5% |
| **Fecal Occult Blood** | 5.3% | 21.7% | 6.3% |

a. ta from NDA volume 1.37, table D- 3. Not all of the subjects had labs available for all

b. This table contains first the number of subjects with available data, and then the percentages of subjects counted with the specified AE. Subjects with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Any individual clinical adverse experience that reached the 5.0% incidence level in any treatment group category was included in this table. If no individual adverse experiences reached the 5.0% level, then just the body system is shown, provided at least 1 patient in any treatment group had an adverse experience in that body system.

8.1.8.10 Adverse events **analysis for drug-drug interactions**

Subjects taking **Warfarin**

Table 18.0.11, found in appendix six, summarizes the clinical AEs in subjects taking warfarin along with tirofiban and/or heparin. Note the very small number of subjects in the tirofiban alone group and the heparin/no procedures group, both drawn from the PRISM trial. This derives, in part, from the common use of ticlid following angioplasty and/or stent placement, such as occurred in the.RESTORE trial. Overall, subjects who received warfarin in the tirofiban plus heparin group had higher clinical event rates compared to subjects in the heparin/procedures group (compare with the incidences of AEs in the overall subject population from tables 8.1.3.1 and 8.1.3.2, p. 199). In particular, postoperative bleeding, hematoma and ecchymosis were higher in the combination group of subjects who received warfarin compared to heparin/procedures subjects on warfarin, and were higher compared to the overall patient population receiving combination therapy. Other AEs, such as epistaxis, anxiety, pelvic pain, and malaise, occurred more often in the warfarin-treated subjects receiving tirofiban than in the corresponding heparin group.

The table below summarizes the lab AEs for subjects taking warfarin. There was an increased incidence in ALT and AST elevations in subjects receiving tirofiban plus heparin therapy compared to heparin alone; these rates, however, were almost identical to those in the overall patient population receiving combination therapy for ALT (compare with the incidences of AEs in the overall subject population from tables 8.1.3.1 and 8.1.3.2 above). Subjects who received warfarin with tirofiban alone had a higher incidence of decreases in hemoglobin and hematocrit and increased fecal occult blood and blood in urine compared to the other treatment groups, but the number of subjects who received warfarin in this group was small. In the tirofiban alone group, urinary blood and decreases in hemoglobin and hematocrit occurred more frequently than the heparin or tirofiban +heparin groups.

Table 8.1.8.10.3 Percentage of subjects receiving warfarin with lab AEs in the phase II-III database[a,b].

| | Tirofiban n=32 | Tirofiban + Heparin n=196 | Heparin n=245 |
|---|---|---|---|
| **Hematology** | 9.4% | 6.7% | 6.6% |
| Eosinophils increased | 3.1% | 0.0% | 0.0% |
| Hematocrit decreased | 6.3% | 1.5% | 1.2% |
| Hemoglobin decreased | 6.3% | 2.1% | 1.7% |
| Platelet count decreased | 0.0% | 1.6% | 2.1% |
| WBC count increased | 3.1% | 2.2% | 1.8% |
| **Chemistry** | 12.5% | 9.8% | 11.1% |
| ALT increased | 3.7% | 3.3% | 2.1% |
| AST increased | 3.7% | 4.7% | 1.9% |
| Serum calcium decreased | 3.7% | 0.6% | 0.5% |
| Serum creatinine increased | 0.0% | 0.0% | 1.7% |
| Serum glucose decreased | 3.7% | 0.5% | 0.0% |
| Serum glucose increased | 0.0% | 1.6% | 0.0% |
| Serum magnesium decreased | 3.6% | 5.0% | 3.9% |
| Serum phosphorus decreased | 0.0% | 0.6% | 1.5% |
| Serum potassium decreased | 0.0% | 2.6% | 3.0% |
| Serum protein decreased | 3.7% | 0.6% | 0.0 |
| **Urinalysis** | 25.8% | 20.1% | 17.1% |
| Urine blood increased | 25.8% | 9.6% | 8.0% |
| Urine glucose increased | 0.0% | 0.7% | 1.6% |
| Urine protein increased | 0.0% | 2.1% | 1.6% |
| **Fecal Occult** Blood | 6.7% | 0.0% | 0.0% |

Data from NDA volume 1.37, table D- . Not all subjects had data available for each test.

b. This table contains percentages of subjects who had the test performed, followed by the percentage of those subjects with the specific AE. Subjects with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Any individual clinical adverse experience that reached the 5.0% incidence level in any treatment group category was included in this table. If no individual adverse experiences reached the 5.0% level, then just the body system is shown, provided at least 1 patient in any treatment group had an adverse experience in that body system.

The sponsor also analyzed the clinical and lab AEs for subjects who received low molecular-weight heparin (LMWH) or thrombolytics. Overall, 111 subjects received LMWH, and 80 received thrombolytics. While there were no obvious differences in the rates for any AEs, the sample size is obviously too small to make definitive statements concerning the risk of tirofiban in combination with these products (see NDA vol. 1.37, tables D-9 1 through D-94 for details).

8.1.8.10 Adverse events analysis for drug-drug interactions

II, Subjects taking cardiovascular drugs (n-blockers, calcium channel-blockers, nitrates)

The tables below summarize the clinical and lab AEs occurring in subjects who the three cardiovascular drugs listed above. Use of these three classes of compounds was common in the phase III trials (see individual study reports for numbers), and no significant differences existed with regard to usage between the study arms (tirofiban, tirofiban+heparin, heparin). The summary of the lab AEs follows the clinical AEs for each of the three drugs.

***Subjects*** faking J-blockers

As shown in table 18.0.12, found in appendix six, no significant differences in the rates of specific AEs in the group taking B-blockers, compared with the total subject population were noted. Increased incidence of hematoma, post-operative bleeding, epistaxis and ecchymoses were noted in the tirofiban groups, similar to the entire subjects database.

The table below summarizes the incidence of lab AEs, according to the use of D-blockers. While the tirofiban groups had increased incidence of blood in the urine and feces, as well as a slightly higher incidence of low platelet counts, these differences were similar to what was seen in the subject database.

Table 8.1.8.10.4 Percentage of subjects receiving B-blockers with lab AEs in the phase II-III database[a,b].

| | Tirofiban n=1450 | Tirofiban + Heparin n=1490 | Heparin n=2654 |
|---|---|---|---|
| **Hematology** | 8.3% | 7.3% | 6.1% |
| Hematocrit decreased | 2.8% | 2.2% | 2.0% |
| Hemoglobin decreased | 3.1% | 1.9% | 2.6% |
| Platelet count decreased | 2.2% | 2.1% | 1.5% |
| WBC count increased | 1.6% | 1.2% | 1.1% |
| **Chemistry** | 5.8% | 11.2% | 8.6% |
| ALTincreased | 0.6% | 3.7% | 3.0% |
| AST increased | 0.8% | 4.3% | 3.0% |
| Serum glucose increased | 1.2% | 0.8% | 0.9% |
| Serum potassium decreased | 1.3% | 3.0% | 1.7% |
| **Urinalysis** | 12.7% | 19.3% | 12.4% |
| Urine blood increased | 9.6% | 10.6% | 6.9% |
| Urine glucose increased | 1.2% | 0.8% | 0.9% |
| Urine protein increased | 2.2% | 1.3% | 1.3% |
| **Fecal Occult Blood** | 10.3% | 19.2% | 8.3% |

a. 1 ta from NDA volume 1.37, table D-99. Not all subjects had data for each test.

b. This table contains percentages of subjects counted. Subjects with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Any individual clinical adverse experience that reached the 5.0% incidence level in any treatment group category was included in this table. If no individual adverse experiences reached the 5.0% level, then just the body system is shown, provided at least I patient in any treatment group had an adverse experience in that body system.

8.1.8.10 Adverse events analysis for drug-drug interactions

Subjects taking calcium channel-blockers *(CCBs)*

As shown in table 18.0.13, found in appendix *six, no* significant differences in the rates of specific AEs in the group taking CCBs, compared with the total subject population were noted. Once again, epistaxis, IV site hemorrhage, post-operative bleeding, and ecchymoses were more common in the tirofiban group.

The table below summarizes the lab AEs occurring for subjects on calcium channel blockers.

Table S.i.8.10.5 Percentage of subjects receiving CCBs with lab AEs in the phase II-III database[a,b].

| | Tirofiban n=957 | Tirofiban + Heparin n=1036 | Heparin n=1768 |
|---|---|---|---|
| Hematology | 8.9% | 7.4% | 6.9% |
| Hematocrit decreased | 2.9% | 2.6% | 2.2% |
| Hemoglobin decreased | 3.0% | 2.5% | 2.7% |
| Platelet count decreased | 1.9% | 1.7% | 1.6% |
| WBC count increased | 1.6% | 1.0% | 1.3% |
| **Chemistry** | 7.3% | 10.4% | 8.2% |
| ALT increased | 1.0% | 3.0% | 2.0% |
| AST increased | 1.1% | 3.1% | 2.0% |
| Serum glucose increased | 1.6% | 0.7% | 1.4% |
| Serum potassium decreased | 1.6% | 2.8% | 2.3% |
| **Urinalysis** | 13.9% | 20.1% | 12. % |
| Urine blood increased | 10.7% | 9.7% | 6.1% |
| Urine glucose increased | 1.3% | 0.7% | 1.1% |
| Urine protein increased | 1.8% | 1.5% | 1.1% |
| Fecal Occult Blood | 11.5% | 15.6% | 5.8% |

a. D t from NDA volume 1.37, table D- Not all subjects bad data for est n test

b. This table contains percentages of subjects with available data, and then the % of those subjects with an abnormal AE. Subjects with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Any individual clinical adverse experience that reached the 5.0% incidence level in any treatment group category was included in this table. If no individual adverse experiences reached the 5.0% level, then just the body system is shown, provided at least 1 patient in any treatment group had an adverse experience in that body system.

Subjects taking nitrates

As shown in table 18.0.14, found in appendix six, no unexpected differences in the rates of specific AEs in the group taking nitrates, compared with the t&l subject population were noted. As in the overall group, bleeding AEs were more common in the tirofiban groups. Note that for some of the bleeding AEs, the % in the tirofiban groups was somewhat larger than in the overall subject population (in particular, epistaxis and ecchymosis).

Table 8.1.8.10.6 Percentage of subjects receiving nitrates with lab AEs i he phase II-II database[a,b].

| | Tirofiban n=1799 | Tirofiban + Heparin n=1835 | Heparin n=3243 |
|---|---|---|---|
| Hematology | 8.4% | 6.9% | 6.7% |
| Hematocrit decreased | 2.7% | 2.1% | 2.1% |
| Hemoglobin decreased | 3.0% | 2.1% | 2.7% |
| Platelet count decreased | 2.2% | 1.8% | 1.5% |
| WBC count increased | 1.7% | 1.1% | 1.3% |
| Chemistry | 5.8% | 10.9% | 8.5% |
| ALT increased | 0.8% | 3.6% | 2.5% |
| AST increased | 1.0% | 4.2% | 2.6% |
| Serum glucose increased | 1.1% | 0.7% | 1.0% |
| Serum potassium decreased | 1.1% | 2.8% | 1.9% |
| **Urinalysis** | 12.5% | 19.4% | 12.7% |
| Urine blood increased | 9.9% | 10.6% | 7.2% |
| Urine glucose increased | 1.1% | 0.9% | 1.1% |
| Urine protein increased | 1.7% | 1.4% | 1.3% |
| Fecal Occult Blood | 10.5% | 18.5% | 7.4% |

a ata from NDA volume 1.37, table J-101. Not all subjects had data for ea test.

8.1.8.10 Adverse events **analysis for** drug-drug **interactions**

Subjects taking non-steroidal anti-inflammatory drugs (NSAIDs)

As shown in table 18.0.15, found in appendix 6, the use of NSAIDs was relatively uncommon in the phase II-III database, with <10% of subjects in each treatment group taking them (see first table below). Per protocol, NSAIDs were to be discontinued prior to entry into the studies, and were not to be initiated during the studies unless medically necessary.

Regarding the clinical AEs, the group of subjects who received NSAIDs appeared to have more chest pain, headache, and nausea, when compared to the entire patient population,. The chest pain and headaches were likely among the indications for administration of NSAIDs, and the nausea/ vomiting may be explained by the well-known gastrointestinal side effects of these agents. Bleeding adverse experiences (hematoma, ecchymoses, hematuria) were increased in the tirofiban plus heparin group compared to heparin/procedures, but were comparable to the overall patient population receiving tirofiban plus heparin. In general, the incidence of clinical AEs in subjects who received tirofiban (with or without heparin) and NSAIDs are comparable to the rates in the population as a whole, suggesting no clinically important additional risk conferred by NSAID use.

The next table summarizes the lab AEs occurring in subjects taking NSAIDs in the safety database. With NSAIDs there was no major increase in urine blood or fecal occult blood in the combination group compared to heparin; however, the tirofiban-alone group appeared to have more fecal occult blood compared to the other groups and compared to the overall patient population receiving tirofiban. Again, there was a slight increase in the incidence of elevated ASTs in the tirofiban plus heparin group.

**Table** 8.1.8.10.7 Percentage of subjects receiving non-steroidal anti-inflammatory drugs with lab AEs in the phase II-III database[a,b].

| | **Tirofiban** n=85 | **Tirofiban + Heparin** n=188 | **Heparin** n=214 |
|---|---|---|---|
| **Hematology** | 6.0% | **5.9%** | **7.9%** |
| Granulocytes increased | **1.2%** | **0.0%** | **0.0%** |
| Hematocrit decreased | **1.2%** | 2.1% | **1.9%** |
| Hemoglobin decreased | **1.2%** | 1.1% | 2.3% |
| Monocytes increased | **1.2%** | 0.0% | 0.0% |
| Neutrophils increased | **0.0%** | 0.0% | 1.0% |
| Platelet count decreased | 2.4% | 0.0% | 1.9% |
| WBC count increased | 1.2% | 1.6% | 2.4% |
| **Chemistry** | 9.4% | 8.6% | 9.0% |
| ALT increased | 2.5% | 3.1% | 3.4% |
| AST increased | 3.8% | 5.2% | 2.1% |
| BUN increased | 2.5% | 0.5% | 0.0% |
| Serum albumin decreased | 0.0% | 1.2% | 0.0% |
| Serum calcium decreased | 0.0% | 0.0% | 1.0% |
| Serum creatinine increased | 1.3% | 0.0% | 0.5% |
| Serum glucose decreased | 1.3% | 0.5% | 0.0% |
| Serum glucose increased | 1.3% | 0.5% | 0.0% |
| Serum phosphorus decreased | 0.0% | 0.0% | 1.1% |
| Serum potassium decreased | 0.0% | 1.1% | 1.0% |
| **Urinalysis** | 13.8% | 25.9% | 15.8% |
| Urine bilirubin increased | 0.0% | 4.5% | 1.2% |
| Urine blood increased | 10.1% | 9.7% | 8.4% |
| Urine protein increased | 3.8% | 1.2% | 1.1% |
| **Fecal Occult Blood** | 17.6% | 4.2% | 4.9% |

a ta from NDA volume 1.37, table D-IO

b. This table contains the percentages of subjects with specific AE. Subjects with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Any individual clinical adverse experience that reached the 5.0% incidence level in any treatment group category was included in this table. If no individual adverse experiences reached the 5.0% level, then just the body system is shown, provided at least I patient in any treatment group had an adverse experience in that body system. Not all subjects had data for each test.

8.2 Summary of Safety Review

Based on the safety database presented in section 8.1 above, the administration of tirofiban is associated with an increased incidence of two adverse events: bleeding; and thrombocytopenia. This review will emphasize the comparison between tirofiban +heparin and heparin alone, as the sponsor proposes using tirofiban in conjunction with heparin.

Bleeding AEs

A total of 7531 subjects, of which 3935 received tirofiban alone or in combination with heparin, were enrolled in the tirofiban phase II-III trials. These subjects provide the safey database used in this review. Overall, sufficient number of subjects were available in most important sub-groups to allow reasonable inferences concerning safety. Exceptions to this statement include small numbers of non-white subjects and subjects with hepatic or renal disease. For these subgroups, the database is inadequate to provide a strong basis for assessing safety.

As reviewed in 8.1, and in Appendix 11, the use of tirofiban, especially in conjunction with heparin, is associated with an increase in the incidence of clinically-significant bleeding. This includes the following observations concerning bleeding risk in the phase II-III population:

1. There was a higher incidence of SAEs for gastrointestinal hemorrhage in the tirofiban +heparin group (0.6%), compared with the total heparin-alone group (~0.1%) and the Heparin/ Procedures group (0.1%) (see table 8.1.2.1, p. 197).

2. There was a higher incidence of bleeding AEs overall in both the tirofiban +heparin and the tirofiban-alone groups, compared with heparin-alone (see table 8.1.3.2, p. 201). In particular, gastrointestinal system and respiratory system bleeding AEs were markedly increased in incidence, compared with the heparin-alone group.

Table 8.2.1 (reproduces table 8.1.3.2) Bleeding adverse events in the phase II-III trials of tirofiban from NDA 20-912[a].

| | Tirofiban + Heparin n=1953 | Heparin/ Procedures n=1887 | Tirofiban n=2032 | Heparin/ No Procedures n=1659 | Total Heparin[b] n=3546 |
|---|---|---|---|---|---|
| **Subjects with bleeding clinical AE** | 1021 (52.3%) | 733 (38.8%) | 424 (20.9%) | 143 (8.6%) | 876 (24.7%) |
| **Subjects without bleeding clinical AE** | 932 (47.7%) | 1154 (61.2%) | 1608 (79.1%) | 1516 (91.4%) | 2670 (75.2%) |
| **Body as a whole** | 1 (0.1%) | 1 (0.1%) | 10 (0.5%) | 9 (0.5%) | 10 (0.3%) |
| **Cardiovascular System** | 844 (43.2%) | 616 (32.6%) | 245 (12.1%) | 86 (5.2%) | 702 (19.8%) |
| Bleeding, postoperative | 659 (33.7%) | 468 (24.8%) | 139 (6.8%) | 34 (2.0%) | 502 (14.1%) |
| Extravasation | 8 (0.4%) | 3 (0.2%) | 13 (0.6%) | 4 (0.2%) | 7 (<0.1%) |
| Hematoma | 206 (10.5%) | 125 (6.6%) | 63 (3.1%) | 26 (1.6%) | 151 (4.2%) |
| Hemorrhage | 24 (1.2%) | 39 (2.1%) | 11 (0.5%) | 3 (0.2%) | 42 (1.2%) |
| Hemorrhage, IV site | 105 (5.4%) | 77 (4.1%) | 61 (3.0%) | 20 (1.2%) | 97 (2.7%) |
| **Digestive System** | 96 (4.9%) | 29 (1.5%) | 53 (2.6%) | 13( 0.8%) | 42 (1.2%) |
| Hematemesis | 17 (0.9%) | 6 (0.3%) | 4 (0.2%) | 0 (0.0%) | 6 (0.2%) |
| Hemorrhage, gastrointestinal | 18 (0.9%) | 4 (0.2%) | 11 (0.5%) | 6 (0.4%) | 10 (0.3%) |
| Hemorrhage, gingival | 19 (1.0%) | 3 (0.2%) | 11 (0.5%) | 3 (0.2%) | 6 (0.2%) |
| Hemorrhage, oral | 28 (1.4%) | 5 (0.3%) | 8 (0.4%) | 0 (0.0%) | 5 (0.2%) |
| **Hemic and Lymphatic System** | 4 (0.2%) | 1 (0.1%) | 5 (0.2%) | 0 (0.0%) | 1 (<0.1%) |
| **Respiratory System** | 125 (6.4%) | 33 (1.7%) | 143 (7.0%) | 21 (1.3%) | 54 (1.5%) |
| Epistaxis | 109 (5.6%) | 20 (1.1%) | 130 (6.4%) | 18 (1.1%) | 38 (1.1%) |
| Hemoptysis | 23 (1.2%) | 11 (0.6%) | 18 (0.9%) | 3 (0.2%) | 14 (0.4%) |
| **Skin and Skin Appendage** | 222 (11.4%) | 154 (8.2%) | 43 (2.1%) | 5 (0.3%) | 159 (4.5%) |
| Ecchymosis | 217 (11.1%) | 153 (8.1%) | 40 (2.0%) | 5 (0.3%) | 158 (4.5%) |
| **Special Senses** | 3 (0.2%) | 0 (0.0%) | 3 (0.1%) | 2 (0.1%) | 2 (<0.1%) |
| Urogenital | 73 (3.7%) | 49 (2.6%) | 29 (1.4%) | 18 (1.1%) | 67 (1.9%) |
| Hematuria | 67(3.4%) | 42 (2.2%) | 26 (1.3%) | 17 (1.0%) | 59 (1.7%) |

a. Data from NDA volume 1.2, Table C-39 and electronic datasets.
b. Includes all subjects from Heparin/ No procedures and Heparin/ Procedures groups.

Bleeding AEs (cont)

Several laboratory indicators of bleeding occur more in the tirofiban +heparin group.

3. There is a larger drop in the mean hemoglobin and hematocrit in the tirofiban +heparin group, compared with heparin (see tables 8.1.4.2.1, and 8.1.4.2.5, p. 202). The incidence of increased urinary and fecal occult blood is also higher in the tirofiban +heparin group (see table 8.1.4.3.1, p. 205).

4. The number of subjects who were discontinued for bleeding AEs is higher in the tirofiban +heparin group: tirofiban +heparin, 3.6%; heparin-alone, 0.73% (see table 8.1.5.2, p. 210). This includes more bleeding AEs due to the following: post-operative bleeding; hematoma formation and GI bleeding AEs (table 8.1.5.3.2, p. 210).

5. The number of PRBC transfusions was higher in the tirofiban +heparin group (3.6%) than in the comparator heparin-alone group (2.4%) and for the entire heparin-alone group (1.2%), see table 8.1.7.1e. 1.1, p. 225.

6. The increased frequency of clinical bleeding events occurred in all almost all body systems (see table 8.1.7.1d.2, p. 226), and were defined as 'Any,' 'Oozing,' or 'Minor.' The occurrence of major bleeding, defined either by protocol or by T&II-classification, was not nominally significantly increased in the tirofiban +heparin group, compared with heparin-alone. However, there was a higher incidence of TIMI-class and protocol-defined major bleeding in the tirofiban +heparin group, in both the PRISM-PLUS and the RESTORE trials (see table 8.1.7.1e.2.1, p. 226). Due to variable rates of bleeding in the control groups, it is difficult to compare the rate of major bleeding in the tirofiban safety database with the rates reported for other GP IIb/IIIa platelet receptor antagonists (see section 8.1.7.1e.3, p. 226).

7. In the PRISM-PLUS trial, bleeding was increased in the tirofiban +heparin group in subjects who did not undergo any cardiac procedures (see table 8.1.7.1e.0.2 and 8.1.7.1e.0.3, pages 223-224), 'and in subjects who underwent cardiac procedures (see 8.1.7.1e.0.4, p. 224). The overall rate of bleeding was significantly higher in the subjects who underwent cardiac procedures (see tables pages 223-224). In this group, the rate of bleeding in the tirofiban +heparin group was higher than the heparin-alone group, and included an increase in severe and life-threatening bleeding events.

8. For life-threatening bleeds (retroperitoneal, intracranial, pericardial), the only obvious difference was in the rate of retroperitoneal bleeding in the RESTORE trial. In that trial, use of tirofiban +heparin was temporally associated with 5 retroperitoneal bleeds (5/1071 =0.47%), compared with 2 in the heparin-alone group (2/1070 = 0.19%) (see table 8.1.7.1e.2.3.1, p. 228). Two of the tirofiban +heparin group (AN 1777, AN 1809) and one of the heparin-alone group (AN 144.5) died.

The incidence of bleeding adverse events was examined in specific subsets of the database.

9. In the PRISM-PLUS trial, the increased bleeding in the tirofiban +heparin group was seen within 48 hours of starting the study drug infusion (table 8.1.7.1e.0.3, p. 224), and occurred regardless of whether an individual had an invasive cardiac procedure or not (tables 8.1.7.1e.0.2 and 8.1.7.1e.0.4, pps. 224-5).

10. No analysis regarding the relationship between the dose of tirofiban and the risk of bleeding was performed (see p. 237 for discussion). Tirofiban was administered using a μg/kg dosing.

11. Subjects who received an overdose of tirofiban had an increased incidence, but not severity, of bleeding, compared to the overall cohort of subjects who received tirofiban or tirofiban plus heparin at doses defmed in the study protocols. This was especially true for epistaxis, IV site bleeding, and GI bleeding (see table 8.1.6.5.2, p. 213).

12. Women had a slightly higher incidence of all adverse events, both bleeding and non-bleeding, as well as more SAEs. For non-bleeding AEs, only vasovagal reactions were disproportionately-increased in the tirofiban groups. Women had a higher incidence of bleeding overall (see table 18.0.5, page 347), especially the following sites: hematoma; 'hemorrhage'; IV site hemorrhage; and epistaxis (shaded in the table). Overall, the incidence of these bleeding events was increased proportionately in both the tirofiban +heparin and the heparin-alone groups.

13. Subjects ≥65 years age had a slightly higher incidence of all adverse events, both bleeding and non-bleeding. Regarding the non-bleeding AEs, death, unstable angina, heart failure, cardiogenic shock, pulmonary edema, constipation, and neurologic/ urologic AEs were increased equally in all treatment groups in the >65 group. Regarding bleeding AEs, analysis of the effect of age on bleeding risk found that the risk of major bleeding increased as age increased (see table 8.1.8.1.5, p. 238, second row), although the interaction was not significant per the sponsor. With regard to specific bleeding events, hematuria, IV site hemorrhage, epistaxis, ecchymoses, and overall hemorrhage were more common in the elderly population, but were increased proportionately in both the tirofiban +heparin and heparin groups (table 18.0.6 page 348).

14. Analysis of the effect of race of adverse event rates is complicated by the small number of non-white subjects in the database: Black 369; Asian, 100; Hispanic 353; Other 240. While no adverse effect of race on any individual clinical event was clearly identified (see table 18.0.3, p. 345), small numbers make definite statements difficult to make.

15. Subjects with impaired renal function who received tirofiban +heparin *were* at non-significantly increased risk of bleeding when compared with heparin alone (see table 8.1.8.1.7, p. *239).* It is also clear that there is an inverse relationship between renal function (as measured by calculated creatinine clearance) and tirofiban clearance (see table 6.2.2.12.3.8, page 241). The details of this relationship are difficult to establish, due to the small number of subjects with impaired renal function in the database (12 with GFR <30 ml/min in the PRISM trial). Dr. Peiayo also reviewed a trial specifically looking at the effect of renal function on tirofiban clearance (see his review).

16. No link between the following diseases and increased incidence of adverse events in the tirofiban +heparin group (relative to heparin alone) were identified: I) Hypertension (see 18.0.7, page 350); 2) Hypercholesterolemia (see table 18.0.8, table 352); and 3) Diabetes (see table 18.0.9, page 353). There was a higher incidence of deaths in the diabetics in all groups, and a higher proportion of diabetics vs. non-diabetics who received tirofiban +heparin and experienced 'nervousness,' relative to the heparin-alone group.

The effect of hepatic disease on the incidence of clinical adverse events was not analyzed. See section 8.1.7.4 for examination of link between abnormal LFTs and clinical adverse events.

17. No drug-drug interactions resulting in an overall increased rate of clinical adverse events was identified for the following drugs, when taken in combination with tirofiban +heparin: I) ticlopidine (table 18.0.10, p. 355); 2) warfarin (table 18.0.11, p. 356); 3) Beta-blockers (table 18.0.12, p. 357); 4) Calcium channel blockers (table 18.0.13, p. 358); 5) nitrates (table i8.0.14, p. 359); 6) NSAIDs (table 18.0.15, p. 360).

For subjects who took warfarin, ecchymoses and hematomas occurred more in the group that received tirofiban +heparin, and were more frequent compared to the overall patient population receiving combination therapy. Post-op bleeding was increased equally in all groups who received war-fat-in in combination with tirofiban and/or heparin. No data is available on the potential interaction of tirofiban and other GP IIb/IIIa inhibitors, and the database on concomitant use of tirofiban and low-molecular weight heparin is quite small (1 I I total subjects).

Thrombocytopenia

The incidence of thrombocytopenia (<90,000 /$mm^3$) *was 1.5%* in the tirofiban +heparin group, 1.2% in the tirofiban-alone group, and 0.6% in the total heparin-alone group (see table 8.1.7.2.1, p. 230). The incidence of marked thrombocytopenia (<20,000 /mm') was similar in the tirofiban +heparin and heparin-alone groups, as was the incidence of platelet transfusion.

No other adverse events were clearly identified which were possibly, probably, or definitely linked to the administration of tirofiban in the entire phase II-III database.

10.0 Conclusions

Tirofiban is an effective inhibitor of platelet aggregation at the doses used in the NDA. The three trials submitted in support of clinical efficacy suggest that there is a beneficial effect of tirofiban on the clinical course of acute ischemic coronary artery disease. With regard to safety, the proposed dose and duration of tirofiban therapy (in conjunction with heparin and aspirin) is associated with an increased incidence of clinically significant bleeding, when compared with the heparin and aspirin (without tirofiban). There is also an association between tirofiban administration and the development of thrombocytopenia.

11.0 Reviewer's Signature

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12.0 References


1. Investigators E. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angiography. *NEJM*. 1994;330:956-961.
2. Investigators C. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancer. 1997;349:1429-1435.
3. Investigators E. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *NEJM*.1997;336:1689-1696.
4. Investigators I-I. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. *Lancet*.1997;349: 1422-1328.
5. Group EI. Long-term protection from myocardial ischemic events in a randomized trial with brief integrin ß3 blockade with percutaneous coronary intervention. *JAMA*.1997;278:479-484.
6. Oler A, Whooley MA, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A Meta-analysis. *JAMA*.1996;276:811-815.
7. Rizik DG, Healy S, Margulis A. A new clinical classification for hospital prognosis of unstable angina pectoris. *American Journal of Cardiology*. 1995;75:993-997.
8. Top01 EJ. Novel antithrombotic approaches to coronary artery disease. *American Journal of Caridology*. 1995;75:27B-33B.
9. Committee CS. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet*. 1996;348:1329-1339.
10. Rao A, PRatt C, Berke A, al e. Thrombolysis in myocardial infarction trial--phase I: hemorrhagic manifestations and changes in plasma fibrinogen and fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J. Amer. Coll. Cardiol.* 1988; 11:1-11.
11. Theroux P, Kleiman N, P.K.Shah. A double-blind, heparin-controlled study of MIX-852 in unstable angina. *Circulation.* 1993;88:I-201.
12. Lincoln AM, Tcheng JE, Califf RM. Standard versus low-dose weight-adjusted heparin in patients treated with the platelet glycoprotein IIb/IIIa receptor antibody fragment abciximab (c7E3 Fab) during percutaneous coronary revascularization. *Amer. Jnl. of Cardiology*. 1997;79:286-29 1.
13. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *NEJM*.1992;326:242-250.
14. Willerson JT, P.Golino, Campbell WB, Buja LM. Specific platelet mediators and unstable coronary artery lesions; experimental evidence and potential clinical implications. *Circulation.* 1989;80:198-205.

## 13.0 Appendix One: Abbreviations And Formulas

The following abbreviations were commonly used in this review.

| | |
|---|---|
| AE | Adverse Event |
| ACT | Activated Clotting Time |
| BTE | Bleeding Time Extension. |
| CABG | Coronary Artery Bypass Graft |
| GP IIb/IIIa | Glycoprotein receptor type IIb/IIIa (on platelets) |
| %IPA | Percent inhibition of platelet aggregation, as stimulated by 5mM ADP |
| PRBC | Packed Red Blood Cells |

PRISM Trial A randomized, parallel, double-blind study to investigate the safety and clinical efficacy of MK-0383 versus heparin in subjects with unstable angina/non-Q-wave myocardial infarction. (protocol 011)

PRISM-PLUS Trial A multicenter, randomized, parallel, double-blind study to investigate the safety and clinical efficacy of MK-0383 in combination with heparin versus heparin alone with high-risk unstable angina/non-Q-wave myocardial infarction. (protocol 006)

PTCA Percutaneous Transluminal Coronary Angioplasty

RESTORE Trial A randomized, double-blind, placebo-controlled study of the effects of tirofiban (MK–0383) on cardiac outcomes in subjects undergoing percutaneous transluminal coronary angioplasty or atherectomy due to unstable angina pectoris or following acute myocardial infarction. (protocol 013).

SAE Serious Adverse Event An AE which results in death, permanent disability or substantial disability, hospitalization, congenital anomaly; or cancer; was life-threatening; or was due to an overdose.

UAP/ NQWMI Unstable Angina Pectoris, Non-Q-wave MI

## 14.0 Appendix Two: subject death narrratives

No subject deaths were reported for three of the protocols that make up the safety database: #005; #007; and #008. Narratives for the subject deaths in the remaining three trials are below, along with tables summarizing the overall crude mortality rates for each of the trials. A total of 209 narratives, provided by the sponsor: are included from the three trials. For another 61 subjects, who died between 30 and 180 days after study drug administration, no details of the cause of death, and no death narratives, are available. A small number of these narratives have been verified by the FDA reviewer through review of the CRFs.

### 14.0.1 Deaths from PRISM-PLUS (protocol #006)

Through 30 days of follow-up, 85 subject deaths had been reported for protocol #006 (A Multicenter, Randomized, Parallel, Double-Blind Study to Investigate the Safety and Clinical Efficacy of MK–0383 Alone, and MK–0383 in Combination With Heparin vs. Heparin Alone in Patients With High-Risk Unstable Angina/Non-Q-Wave Myocardial Infarction, PRISM-PLUS). At the end of the 180 day follow-up, there were 134 reported deaths. The table below summarizes these deaths by treatment group and time of reporting.

Table 8.1 .l.ld.l Deaths in the PRISM-PLUS trial"

| Time of Follow-up | Tirofiban alone n=345 | Tirofiban + Heparin n=773 | Heparin alone n=797 | Total n=1915 |
|---|---|---|---|---|
| 48 hours | 2 (0.6%) | 1 (0.1%) | 2 (0.2%) | 5 (0.3%) |
| 7 days | 16 (4.6%) | 15 (1.9%) | 15 (1..9%) | 46 (2.4%) |
| 30 days | 21 (6.1%) | 28 (3.6%) | 36 (4.5%) | 85 (4.4%) |
| 180 days | 25 (7.2%) | 53 (6.9%) | 56 (7.0%) | 134 (7.0%) |

a. Data from NDA volume 1.42, tables 17-20.

Subject death narratives from PRISM-PLUS:

Narratives of circumstances leading to death were provided by the sponsor for the 85 deaths (2 1 tirofiban, 28 tirofiban plus heparin, and 36 heparin) that occurred during the study drug infusion period and up to Day 30 after randomization. Five additional deaths (subjects #6990 and #7001 in the combination group; subjects #5293, #643 1, and #7802 in the heparin group) occurred outside the 30-day reporting period, but included in the SAEs, and their death narratives are included in the summary of causes of death below.

No subject narratives, and no details as to cause of death are available for 44 additional deaths that occurred after 30 days and before 180 days.

Tirofiban Group

1. Protocol/Study No. 006-008, AN 5098: This 71-year-old male, status post-CABG, myocardial infarction, and abdominal aortic aneurysm repair received open-label heparin prior to randomization to tirofiban alone. On Day 3, study drug was discontinued due to recurrent chest pain and open-label heparin was resumed. Cardiac catheterization on Day 4 revealed severe triple-vessel disease with total occlusion of two of three grafts. Intra-aortic balloon pump was inserted for recurrent ischemic chest pain. Chest x-ray showed evidence of heart failure. Consideration of CABG was prolonged due to discussion of several clinical issues and on Day 5 the patient was intubated and treated with curare. He developed ischemic bowel, hypotension, sepsis, oliguria, elevated serum creatinine and potassium, and acidosis. He was declared "Do not resuscitate" by the family, following which he developed coffee-ground gastric secretions and electromechanical dissociation. He died on Day 7 of ischemic bowel. The investigator felt that the events were unrelated to study therapy.

2. Protocol/Study No. 006-008, AN 5146: This 76-year-old male with no prior known coronary artery disease was initially treated with open-label heparin prior to randomization to tirofiban alone. On Day 3 he developed ischemic chest pain, hypotension, and sinus bradycardia; study drugs were stopped and open-label heparin was resumed. The patient progressed to cardiogenic shock and, despite aggressive resuscitative measures including complicated tracheal intubation, vasopressors, and intra-aortic balloon pump, the patient died on Day 3. Autopsy showed massive infero-posterior myocardial infarction involving posterior papillary muscle and acute pulmonary edema. The investigator felt that the events were unrelated to study therapy.

3. Protocol/Study No. 006-053, AN 5165: This 66-year-old male with a history of diabetes mellitus and history of myocardial infarction and CABG received study infusion of tirofiban alone until Day 3. On the day following randomization, the cardiac enzymes were elevated and there was electrocardiographic evidence of posterior wall myocardial infarction, and the patient developed cardiogenic shock. This progressed to pulmonary edema and cardiac arrest, and the patient died on Day 3. The investigator felt that the events were unrelated to study therapy.

14.0.1 Death Narratives from PRISM-PLUS (protocol #006) (cont)

Tirofiban Group (cont)

4. Protocol/Study No. 006-047, AN 5177: This 69-year-old female received open-label heparin prior to randomization to tirofiban. She underwent cardiac catheterization which revealed multivessel disease and completed the study infusions on Day 4. While waiting for discharge the next morning, she was found to be in cardiorespiratory arrest. Resuscitation measures failed and the patient died on Day 5, presumably due to arrhythmic sudden cardiac death. No autopsy was done. The investigator felt that none of the events was related to study therapy.

5. Protocol/Study No. 006-067, AN 5264: This 65-year-old female with diabetes mellitus, hypertension, and coronary artery disease received study infusion of tirofiban alone until Day 4. Angiography on Day 4 revealed severe triple vessel disease. Following catheterization, the patient developed recurrent refractory ischemia and open-label heparin was started. Urgent coronary bypass surgery was accomplished on Day 5 with an intra-aortic balloon pump inserted postoperatively. On Day 6, the intra-aortic balloon pump was removed and the patient underwent a right lower leg thrombectomy. The patient deteriorated into cardiogenic shock, suffered a cardiac *arrest,* and died on Day 6. The presumed cause of death was circulatory collapse possibly related to acute graft closure. The investigator felt that none of the events was related to study therapy.

6. Protocol/Study No. 006-045, AN 6057: This 61-year-old man received study infusion of tirofiban alone until Day 5. Augiography on Day 3 revealed triple-vessel disease with abnormal left ventricular wall motion. Recurrent chest pain developed on Day 5, progressing to cardiogenic shock and death on Day 6. The investigator felt that none of the events was related to study therapy.

7. Protocol/Study No. 006-033, AN 6131: This 69-year-old male, smoker with first degree AV block, syncope, and history of myocardial infarction was 'initially treated with open-label heparin prior to randomization to tirofiban alone. Study drug was administered for 4 days. Coronary angiography on Day 5 demonstrated severe triple-vessel disease and CABG was scheduled, but the patient developed angina, bradycardia, hypotension, and arrhythmia, and died of cardiogenic shock on Day 5. The investigator felt that none of the events was related to study therapy.

8. Protocol/Study No. 006-033, AN 6166: This 81-year-old female with history of myocardial infarction was treated with open-label heparin prior to randomization to tirofiban alone. Study drug was administered for 4 days. On Day 7, during coronary augiogram dye injection, she developed hypotension and asystole and died despite reanimation efforts. The investigator felt that the cause of death was coronary artery obstruction, and that none of the events was related to study therapy.

9. Protocol/Study No. 006-036, AN 6236: This 59-year-old male asthmatic smoker with a history of peptic ulcer disease received study infusion of tirofiban alone until Day 4. On Day 5 the patient developed shortness of breath with progressive deterioration to cardiac arrest with electromechanical dissociation on Day 6. A pulmonary embolism was suspected and streptokiuase was administered without success. The patient died on Day 6. Autopsy confirmed the cause of death as pulmonary embolism. The investigator felt that none of the events was related to study therapy.

10. Protocol/Study No. 006-044, AN 6250: This 73-year-old male smoker with chronic obstructive pulmonary disease, bronchitis, hypertension, nausea and vomiting, and a history of myocardial infarction received study infusion of tirofiban alone until Day 4. On Day 4, angiography revealed single-vessel disease that was subsequently treated by uncomplicated PTCA. The same day the patient experienced abdominal pain, rectal hemorrhage, and a drop in hemoglobin On Day 5, with signs of peritoneal irritation, the patient suddenly developed electromechanical dissociation and died. Autopsy was refused and the cause of the GI bleed was presumed to be mesenteric ischemia. The investigator felt that none of the events was related to study therapy.

11. Protocol/Study No. 006-045, AN 6290: This 66-year-old female with a medical history including atria1 fibrillation, aortic stenosis, hypertension and cardiovascular disease received open-label heparin prior to randomization to tirofiban alone. One hour and 20 minutes after stopping heparin and starting tirofiban, the patient developed atria1 fibrillation. An evolving myocardial infarction was suspected so tirofiban was stopped and open-label heparin was resumed. Creatine phospholcmase (CPK) levels of Day 3 suggested a posteroinferior M.I. She did well until 3 days later when she abruptly went into convulsions, lost consciousness and died (Day 4), due to left ventricular rupture. No autopsy was done. The investigator felt that none of the events was related to study therapy.

12. Protocol/Study No. 006-037, AN 6340: This 68-year-old male with hypertension, diabetes mellitus, peripheral vascular disease, chronic renal failure, status post-CABG and peptic ulcer disease, received study infusion of tirofiban alone until Day 4. On Day 10, elective CABG was accomplished with an intra-aortic balloon pump and positive inotropic medications required postoperatively. The patient developed electromechanical dissociation with cardiogenic shock, then recurrent ventricular fibrillation, and asystole and died on Day IO. The investigator felt that none of the events was related to study therapy.

14.0.1 Death Narratives from PRISM-PLUS (protocol #006) (cont)

Tirofiban Group (cont)

13. ProtocoUStudy No. 006-034, AN 6524: This 83-year-old female with hypertension, peripheral vascular disease, M.I. X2 and cardiac arrhythmias received open-label heparin prior to randomization to tirofiban alone. Study drug was administered until Day 3. On Day 2, she suffered a myocardial infarction. On Day 3, she suffered more chest pain, became hypotensive, and died of cardiogenic shock. The investigator felt that none of the events was related to study therapy.

14, Protocol/Study No. 006-050, AN 6547: This 61-year-old female with hypertension and history of CABG received prestudy open-label heparin followed by a study infusion of tirofiban alone until Day 4. Coronary angiography on Day 4 revealed triple-vessel disease and graft stenosis. On Day 8, patient underwent CABG complicated by major bleeding. She died later on Day 8 of cardiogenic shock. The investigator felt that none of the events was related to study therapy.

15. ProtocoUStudy No. 006-034, AN 6595: This 70-year-old female with hypertension, diabetes mellitus, ventricular arrhythmias, status post CABG received study infusion of tirofiban alone until Day 4. On Day 2, she developed a new non-Q-wave myocardial infarction. Recurrent angina prompted angiography on Day 8. On Day 9, she developed respiratory distress with severe chest pain and hemodynamic instability and died of an acute M.I. The investigator felt that none of the events was related to study therapy.

16. Protocol/Study No. 006-057, AN 6615: This 81-year-old male with hyperglycemia and history of myocardial infarction received open-label heparin prior to randomization to tirofiban alone. The patient ruled in for a myocardial infarction. Due to a progressive decrease in platelet counts over the next 2 days, tirofiban was discontinued on Day 3. The next day the patient felt fatigued and developed hypoglycemia and, despite treatment, was later found to be unconscious. He then became severely bradycardic, went into electromechanical dissociation, and cardiogenic shock, and died on Day 4. An autopsy confirmed the cause of death as the massive myocardial infarction and cardiogenic shock. The investigator felt that none of the events was related to study therapy.

17. ProtocoUStudy No. 006-032, AN 6623: This 77-year-old female smoker with right bundle branch block, chronic obstructive pulmonary disease, and a history of myocardial infarction, bradycardia, and sinus tachycardia, received open-label heparin prior to randomization to tirofiban alone. On Day 2, she developed left anterior hemiblock, complete AV block, and asystole and a pacemaker was implanted on Day 3 (study therapy was interrupted temporarily). She suffered a nonhemorrhagic cerebrovascular accident during coronary angiography on Day 4 and study drug was discontinued. On Day 5, she developed ventricular fibrillation and died (no resuscitation was attempted due to patient request). The investigator felt that none of the events was related to study therapy.

18. Protocol/Study No. 006-050, AN 6695: This 82-year-old female with hypertension, hypothyroidism, ventricular insufficiency, myocardial infarction, and history of cerebral vascular disease, was started on open-label heparin before randomization to tirofiban alone. On Day 4, the patient experienced ischemic chest pain and underwent angiography which revealed severe triple-vessel disease with left ventricular dysfunction. Study therapy was stopped on Day 4. The patient developed pulmonary edema on Day 6, deteriorating to cardiogenic shock and death on Day 7. The investigator felt that none of the events was related to study therapy.

19. Protocol/Study No. 006-044, AN 7072: This 49-year-old male with a history of CABG x 2 received study infusion of tirofiban alone. On Day 4, study drug was stopped and angiography was performed, during which the patient developed ventricular tachycardia. CABG was performed on Day 11 for recurrent chest pain. On Day 27, the patient developed recurrent ventricular fibrillation unresponsive to resuscitative measures and died early on Day 28. The investigator felt that none of the events was related to study therapy.

20. ProtocoUStudy No. 006-048, AN 7240: This 75-year-old male with a history of hypertension and claudication received study infusion of tirofiban alone. Angiography on Day 3 revealed single-vessel disease with a left ventricular ejection fraction of 47%. Following the procedure the study drugs were completed and the patient developed signs and symptoms of septicemia plus pulmonary edema. Acinetobacter anitratus was isolated from the sputum. Despite antibiotic therapy, the patient deteriorated and died of septicemia on Day 17. The investigator felt that none of the events was related to study therapy.

21. ProtocoUStudy No. 006-086, AN 7530: This 80-year-old male received open-label heparin prior to randomization to tirofiban alone. Study drugs were completed uneventfully on Day 4 after augiography revealed left main and right coronary artery disease. The patient preferred medical management and open-label heparin was started. On the same day, the patient developed severe ischemia, pulmonary edema and cardiogenic shock. A myocardial infarction was suspected; however the patient died (Day 5) before ECG or enzymes could be obtained. No autopsy was done. The cause of death was presumed to be a myocardial infarction. The investigator felt that none of the events was related to study therapy.

14.0.1 Death Narratives from PRISM-PLUS (protocol #006) (cont)

Tirofiban Plus Heparin Group

1. Protocol/Study No. 006-062, AN 1013: This 72-year-old female with coronary, carotid, and peripheral arterial disease, left ventricular hypertrophy, and history of CABG received study infusion of low-dose tirofiban plus heparin until Day 4. Angiography on Day 7 revealed significant triple-vessel and graft disease and medical therapy was elected. The patient was discharged on Day 9. On Day 25, the patient was readmitted with unstable angina complicated by anemia, and was treated with nitrates, heparin, and transfusions. On Day 26, the patient experienced an episode of sinus bradycardia followed by asystole and was resuscitated. The ECG showed accentuation of ST-segment depression and she suffered another cardiac arrest and died on Day 26. The investigator felt that the events were not related to study therapy.

2. Protocol/Study No. 006-050, AN 1034: This 78-year-old female received open-label heparin prestudy followed by study therapy of low-dose tirofiban plus heparin for 3 days. On Day 2, pulmonary overload, confirmed by chest x-ray, was treated with Lasix. On Day 3, while still on study infusions, the patient suddenly developed bradycardia followed by asystole. Resuscitation was unsuccessful and the patient died on Day 3. The investigator felt that none of the events was related to study therapy.

3. Protocol/Study No. 006-036, AN 1147: This 75-year-old male with hypertension, renal artery stenosis, and history of myocardial infarction and aortofemoral bypass received study therapy of low-dose tirofiban plus heparin. Angiography on Day 4 revealed triple-vessel and left main coronary artery disease. Study therapy was successfully completed and the patient was transferred for urgent CABG. Postoperatively the patient developed refractory ventricular fibrillation and could not be resuscitated and died on Day 4. The investigator felt that none of the events was related to study therapy.

4. Protocol/Study No. 006-036, AN 1150: This 85-year-old female with hypertension, status post femoral-popliteal bypass received prestudy open-label heparin followed by study infusion of low-dose tirofiban plus heparin until Day 5. During the course of the infusion, she experienced repetitive episodes of chest pain, reported as refractory ischemia. On Day 4, a myocardial infarction was diagnosed. On Day 5 coronary angiography revealed severe triple-vessel disease with moderate to severe left ventricular dysfunction and the patient was taken urgently to CABG. Postoperatively the patient suffered hypotension, and asystole, and died from perioperative heart failure on Day 5. The investigator felt that none of the events was related to study therapy.

5. Protocol/Study No. 006-035, AN 1264: This 73-year-old male with hypertension, status postmyocardial infarction x 2 and aortoiliac and femoral-popliteal bypass, received study infusion of low-dose tirofiban plus heparin. On Day 3, coronary angiography revealed double-vessel disease with decreased left ventricular ejection fraction of 28%. Study infusions were completed on Day 3, and later the patient developed prolonged angina with secondary CPK increase. Electrocardiographic ischemia persisted and the patient developed a recurrent myocardial infarction on Day 6 complicated by congestive heart failure and cardiogenic shock. The patient died on Day 7. The investigator felt that none of the events was related to study therapy.

6. Protocol/Study No. 006-035, AN 1274: This 79-year-old male with hypertension, status postmyocardial infarction, PTCA, and carotid endarterectomy received prestudy open-label heparin followed by study infusion of low-dose tirofiban plus heparin. Coronary angiography on Day 4 revealed left main and right coronary artery disease and study infusions were completed. On Day 8, the patient underwent CABG. On Day 9, the patient died from postsurgical cardiogenic shock. The investigator felt that none of the events was related to study therapy.

7. Protocol/Study No. 006-062, AN 1293: This 77-year-old male with hypertension, chronic renal insufficiency, left ventricular hypertrophy, peripheral vascular disease, and history of hypothyroidism and bradycardia received prestudy open-label heparin followed by study infusion of low-dose tirofiban plus heparin until Day 4. On Day 5, the patient suffered a new non-Q-wave myocardial infarction complicated by severe pulmonary edema. Angiography on Day 7 revealed triple-vessel disease. An intra-aortic balloon pump was inserted and the patient was taken emergently to CABG. Postoperatively, the patient died from acute pulmonary edema on Day 7. The investigator felt that none of the events was related to study therapy.

8. Protocol/Study No. 006-095, AN 1536: This 76-year-old male with hypertension, diabetes mellitus, status post-CABG received study infusion of low-dose tirofiban plus hepaiin until Day 5. On Day 5, the patient underwent coronary angiography and developed renal failure. On Day 7, the patient developed cardiogenic shock and died of cardiac arrest. The investigator felt that none of the events was related to study therapy.

9. Protocol/Study No. 006-095, AN 1567: This 72-year-old male with hypertension and history of heart failure and M.I. received prestudy open-label heparin followed by study infusion of low-dose tirofiban plus heparin until Day 4. On Day 4, the patient developed recurrent angina. Angiography revealed severe left coronary disease. CABG was performed on Day 9 complicated by low cardiac output. On Day 11, the patient experienced electromechanical dissociation and cardiac arrest. Echocardiogram revealed cardiac tamponade and the patient died on Day 1 I of cardiac arrest. The investigator felt that none of the events was related to study therapy.

14.0.1 Death Narratives from PRISM-PLUS (protocol #006) (cont)

Tirofiban Plus Heparin Group

10. Protocol/Study No, 006-034, AN 1610 This 81-year-old male with peripheral vascular disease, carotid vascular disease, and aortic murmur received study infusion of low-dose tirofiban plus heparin until Day 5. On Day 2, an echocardiogram revealed severe aortic stenosis. On Day 5, the electrocardiogram showed signs of a myocardial infarction. The patient deteriorated and died of a cardiac arrest on Day 6. Autopsy confirmed the aortic stenosis, possible infero-posterior ischemic lesion, and pulmonary edema. The investigator felt that none of the events was related to study therapy.

11. Protocol/Study No. 006-078, AN 1707: This 76-year-old female with angina and heart failure received study infusion of low-dose tirofiban plus heparin until Day 4. On Day 9, the patient experienced cardiogenic shock and died. The investigator felt there was no relationship between the events and the study therapy.

12. Protocol/Study No. 006-102, AN 5579: This 83-year-old male with diabetes mellitus and history of carotid bypass surgery received prestudy open-label heparin followed by study infusion of low-dose tirofiban plus heparin. Angiography on Day 3 revealed severe inoperable triple-vessel disease with markedly reduced left ventricular ejection fraction. On Day 4, study therapy was discontinued and the patient was placed on open-label heparin. On Day 5, the patient developed hypotension progressing to signs of congestive heart failure on Day 7. On Day 8, the patient died of cardiogenic shock secondary to ischemic cardiomyopathy from severe coronary artery disease. The investigator felt that none of the events was related to study therapy.

13. Protocol/Study No. 006-102, AN 5604: This 61-year-old male with hypertension and abdominal aortic aneurysm, status post-CVA, myocardial infarction, and CABG received prestudy open-label heparin followed by study infusion of low-dose tirofiban plus heparin. On Day 3, the patient fell getting out of bed and experienced worsening of pre-existing back pain. Because of the worsening pain, a computerized atria1 tomography scan was performed which revealed a fractured his L1 vertebrae. Angiography on Day 3 revealed severe inoperable triple-vessel disease and the study drugs were discontinued. On Day 5 the patient developed confusion that was felt to be related to pain medications, and acute renal failure felt to be precipitated by the angiography dye. He underwent emergent dialysis. On Day 6, with increasing electrolyte imbalance, a dissection of the thoracic aorta was diagnosed by x-ray (corroborated by transesophageal echocardiogram). The patient was placed on a ventilator, lost all renal function and perfusion to his lower extremities, and went into metabolic acidosis. He died on Day 7 from complications of the aortic dissection. The investigator felt that none of the events was related to study therapy.

14. Protocol/Study No. 006-037, AN 6080: This 69-year-old female with peripheral vascular disease, cerebral vascular disease, abdominal aortic aneurysm and left ventricular hypertrophy, status postmyocardial infarction and CABG, received open-label heparin prior to randomization to low-dose tirofiban plus heparin. Study drugs were discontinued on Day 4. Coronary angiography revealed significant aortic stenosis, left main and right coronary artery occlusions, mitral insufficiency, and carotid stenosis. An intra-aortic balloon pump was inserted, and on Day 5, the patient underwent CABG after which she died from cardiogenic shock. The investigator felt that none of the events was related to study therapy.

15. Protocol/Study No. 006-048, AN 6430: This 64-year-old male with diabetes mellitus was randomized to low-dose tirofiban plus heparin. Study drugs were discontinued on Day 4, and cardiac surgery was scheduled. On Day 6, the patient developed *Staphylococcus aureus* sepsis, acute precordial pain, severe hypotension, and electromechanical dissociation, and died after an IABP was inserted and resuscitation attempted. The cause of death was felt to be cardiogenic shock. The investigator felt that none of the events was related to study therapy.

16. Protocol/Study No. 006-029, AN 6473: This 74-year-old male with diabetes mellitus, chronic bronchitis, extra ventricular systoles, and history of heart failure and myocardial infarction, received intravenous heparin prior to randomization to study infusion of low-dose tirofiban plus heparin. The study infusions were discontinued prematurely at hour 28 due to hematemesis (not considered a serious AE) The patient was discharged on Day 5. The patient died suddenly at home on Day 17. The investigator felt that none of the events was related to study therapy.

17. Protocol/Study No. 006-057, AN 6564: This 89-year-old male with history of myocardial infarction received open-label heparin prior to being randomized to tirofiban and heparin. On Day 2, the patient ruled in with a non-Q-wave myocardial infarction and continued to receive study drugs uneventfully through Day 4. Two days after drug cessation, the patient's condition deteriorated abruptly and he died (Day 6), presumably due to ventricular arrhythmia. The investigator felt that none of the events was related to study therapy.

14.0.1 Death Narratives from PRISM-PLUS (protocol #006) (cont)

Tirofiban Plus Heparin Group (cont)

18. ProtocoUStudy No. 006-049, AN 6591: This 75-year-old female with hypertension, diabetes mellitus, left ventricular hypertrophy, and history of myocardial infarction received heparin prior to randomization to low-dose tirofiban plus heparin. Study infusions were completed on Day 5, and the patient was put back on open-label heparin until CABG was performed on Day 9. Post-CABG the patient developed hypotension, ventricular tachycardia, and excessive blood loss. Resuscitation was unsuccessful, and the patient died on Day 9. The investigator felt that none of the events was related to study therapy.

19. Protocol/Study No. 006-041, AN 6717: This 94-year-old female with a history of urinary tract infection and mastectomy and hypertension received prestudy open-label heparin followed by study infusion of low-dose tirofiban plus heparin. The patient suffered a non-Q-wave myocardial infarction prior to randomization. On Day 2, she developed evidence of a pericardial friction rub and study drug was discontinued in order to use nonsteroidal anti-inflammatory drugs. Recurrent chest pain prompted cardiac catheterization on Day 3, revealing left main coronary artery stenosis. Conservative medical therapy was chosen, The patient's condition progressively worsened with hypotension and oliguria, and on Day 4 she developed cardiogenic shock. She died on Day 5. The investigator felt that none of the events was related to study therapy.

20. ProtocoUStudy No. 006-034, AN 6906: This 77-year-old male with sinus bradycardia, peripheral vascular disease, aortic stenosis, abdominal aortic aneurysm, and left ventricular hypertrophy, status postmyocardial infarction and CABG, received prestudy open-label heparin prior to randomization to low-dose tirofiban plus heparin. On Day 3, he experienced hypotension secondary to left ventricular dysfunction. Study drugs were discontinued on Day 4. On Day 6, he suffered an acute inferior rnyocardial infarction that prompted urgent coronary angiography. This procedure was complicated by cardiogenic shock and ventricular fibrillation and death (Day 6). The investigator felt that none of the events was related to study therapy.

21. Protocol/Study No. 006-044, AN 7020: This 70-year-old male with 'signs of heart failure, carotid murmur, and history of CABG and thrombolysis received prestudy open-label heparin followed by study infusion of low-dose tirofiban plus heparin. Angiography revealed severe triple-vessel disease plus graft stenosis, and the study infusions were discontinued on Day 4. On Day 8, the patient developed recurrent chest pain with hypotension, deteriorating to cardiogenic shock and AV block. The patient died on Day 8. No autopsy was performed. The cause of death was presumed to be a new inferior myocardial infarction leading to cardiogenic shock. The investigator felt that none of the events was related to study therapy.

22. Protocol/Study No. 006-033, AN 7110: This 78-year-old female with hypertension, heart failure, diabetes mellitus, chronic obstructive pulmonary disease, and history of myocardial infarction received study infusion of low-dose tirofiban plus heparin. Study infusions were completed on Day 4, and on Day 8, angiography revealed severe triple-vessel disease. The patient remained in the hospital and was placed on open-label heparin from Day 15 through Day 27. On Day 26, she developed moderate heparin-induced thrombocytopenia (not considered a serious AE) from which she recovered. On Day 28, the patient experienced severe recurrent chest pain, which developed into an acute myocardial infarction with underlying pulmonary edema and was treated with streptokinase. On Day 29, the patient deteriorated into cardiogenic shock and died on Day 30. The investigator felt that none of the events was related to study drug.

23. Protocol/Study No. 006-048, AN 7243: This 77-year-old female with a history of myocardial infarction and atria1 fibrillation received prestudy open-label heparin followed by study infusion of low-dose tirofiban plus heparin until Day 3. On Day 3, the patient developed a new myocardial infarction and was treated with thrombolytic therapy and open-label heparin. On Day 4, the patient developed catheter site bleeding that required transfusions. On Day 5, due to hemodynamic instability requiring an intra-aortic balloon pump and mechanical ventilation, an emergent CABG was performed. The patient developed postoperative cardiogenic shock and subsequently died on Day 9. The investigator felt that none of the events was related to study therapy.

24. ProtocoUStudy No. 006-092, AN 7483: This 77-year-old male with hypertension was randomized to low-dose tirofiban plus heparin. Angiography, PTCA, and atherectomy were performed on Day 4. On Day 5, study drugs were stopped. On the same day, the patient experienced abdominal pain with signs of peritoneal irritation, and a nasogastric tube was inserted. The patient progressed to develop cardiogenic shock, ventricular fibrillation, and death on Day 5. The adverse event report suggests the patient experienced some GI bleeding. The investigator felt that none of the events was related to study therapy.

25. Protocol/Study No. 006-086, AN 7553: This 78-year-old male status postcardiac arrest with a history of hypertension and hypothyroidism received study infusion of low-dose tirofiban plus heparin. On Day 2, while on the toilet, the patient suffered severe bradycardia and hypotension and cardiac arrest. Despite resuscitative efforts, he deteriorated into electromechanical dissociation, and asystole, and died. The investigator felt that none of the events was related to study therapy.

14.0.1 Death Narratives from PRISM-PLUS (protocol #006) (cont)

Tirofiban Plus Heparin Group (cont)

26. Protocol/Study No. 006-092, AN 7644: This 77-year-old female received study infusion low-dose tirofiban plus heparin. On Day 4, angiography revealed left main coronary disease and the study drugs were discontinued for CABG. Postoperatively the patient developed a urinary tract infection, nosocomial pneumonia, and septic shock (Day 5) and was placed on antibiotics. The patient deteriorated into hemodynamic instability from septic shock and subsequently died on Day 10. The investigator felt that none of the events was related to study therapy.

27. Protocol/Study No. 006-092, AN 7648: This 54-year-old female randomized for acute myocardial infarction received study infusion of low-dose tirofiban plus heparin until Day 4. On Day 8, following stent placement, the patient developed an acute reocclusion of a coronary artery, experienced an acute M.I., and deteriorated to cardiogenic shock and death on Day 9. The investigator felt that none of the events was related to study therapy.

28. Protocol/Study No. 006-084, AN 7800: This 59-year-old male with coronary artery disease, asthma, and peripheral vascular disease received study infusion of low-dose tirofiban plus heparin until Day 4. Angiography on Day 4 revealed severe triple-vessel disease. CABG was performed on Day 9. On Day 12, the patient died suddenly of a myocardial rupture. The investigator felt that none of the events was related to study therapy.

Heparin Group

1. Protocol/Study No. 006-034, AN 1054: This 75-year-old female with hypertension, atria1 fibrillation, diabetes mellitus, and hematmia received open-label heparin prior to randomization to study infusion of heparin. On Day 1, the patient developed pulmonary edema. Following angiography on Day 4, acute pulmonary edema recurred, accompanied by heart failure. The patient stabilized and study infusions were completed on Day 4. A new myocardial infarction was diagnosed. On Day 11, following CABG, the patient suffered recurrent heart failure with acute pulmonary edema complicated by cardiogenic shock. The patient died on Day 11. The investigator felt that the events were not related to study therapy.

2. Protocol/Study No. 006-044, AN 1067: This 86-year-old female with hypertension, heart failure, left ventricular hypertrophy, aortic valve stenosis, renal insufficiency, and premature ventricular contractions, received study infusion of heparin until Day 4. The patient was discharged on Day 16. She was readmitted on Day 24 to another hospital for a fractured right knee. On Day 25, the patient suffered a myocardial infarction complicated by pulmonary edema, respiratory arrest, and cardiogenic shock. On Day 26, she developed anemia secondary to bleeding at the fracture site, and was transfused. The patient died on Day 27. The investigator felt that these events were not related to study drug.

3. Protocol/Study No. 006-084, AN 1234: This 69-year-old male with peripheral vascular disease and history of myocardial infarction was randomized to study infusion of heparin. On Day 3, he developed right groin pain that progressed to a bruise at the injection site. By Day 4, he developed chest pain with ischemia, fatigue, abdominal pain, and a bruise. A retroperitoneal bleed was suspected (later confirmed by ultrasound) and the study therapy was stopped. Subsequently he suffered a cardiovascular collapse, was intubated, and died on Day 4. An autopsy confirmed a severely atherosclerotic aorta, a ruptured aortic aneurysm and new myocardial infarction. The investigator felt that the aneurysm rupture was unrelated to study therapy.

4. Protocol/Study No. 006-037, AN 1303: This 66-year-old male with hypertension, diabetes mellitus, atria1 fibrillation, hematuria, and a history of myocardial infarction received study infusion of heparin until Day 4. Following completion of study drugs, angiography revealed triple-vessel disease. On Day 9, the patient underwent CABG. On Day 11, the patient was diagnosed by scan as having a right cerebral vascular accident. On Day 12, following instillation procedure, the patient experienced a cardiorespiratory arrest and died. This was presumed to be from a probable massive myocardial infarction. The investigator felt that none of the events was related to study therapy.

5. Protocol/Study No. 006-089, AN 1541: This 65-year-old male with hypertension and history of myocardial infarction and CABG received study infusion of heparin. The patient had recurrent episodes of angina and became refractory on Day 3. Angiography revealed severe coronary disease. Following the procedure the patient experienced cardiogenic shock and study infusions were discontinued (Day 3). On Day 10, the patient died of a cardiorespiratory arrest. The investigator felt that the events were unrelated to study drug.

6. Protocol/Study No. 006-095, AN 1566: This 63-year-old male with hypertension, heart failure, and history of myocardial infarction received prestudy open-label heparin followed by study infusion of heparin. Study therapy was successfully completed on Day 4. On Day 7, prior to undergoing bypass surgery, the patient experienced recurrent angina and later that day suffered a cardiorespiratory arrest and died. The investigator did not feel that any of the events were related to study therapy.

14.0.1 Death Narratives from PRISM-PLUS (protocol #006) (cont)

Heparin Group

7. Protocol/Study No. 006-045, AN 1654: A 74-year-old female with a history of hypertension and coronary artery disease received prestudy open-label heparin followed by study infusion of heparin until Day 3. On Day 11, angiography showed severe triple-vessel disease and a left ventricular ejection Ii-action of 48%. The same day the patient suffered an acute myocardial infarction. An intra-aortic balloon pump was placed and the patient underwent CABG on Day 13. Postoperatively the patient was profoundly hypotensive and died. The investigator felt that none of the events was related to study drugs.

8. Protocol/Study No. 006-045, AN 1658: This 85-year-old male with a history of hypertension, angina, and isolated PVC's received prestudy open-label heparin followed by study infusion of heparin until Day 4. During the infusion, he experienced repetitive chest pain. On Day 4, following completion of study drugs, a prolonged episode was diagnosed as an acute myocardial infarction. On Day 7, accompanied by further chest pains, the patient became hypotensive, dyspneic, and deteriorated to cardiogenic shock, ventricular tachycardia, ventricular fibrillation, asystole, and death The investigator felt that none of the events was related to the study therapy.

9. **Protocol/Study** No. 006-008, AN 5141: This 62-year-old male with hypertension and left ventricular dysfunction received study infusion of heparin until Day 4. Following completion of study drugs, the patient had recurring chest pain. Angiography revealed severe diffuse coronary artery disease. CABG was performed on Day 7, and in the recovery room the patient suddenly became hypotensive and went into cardiogenic shock and died. The cause of death was presumed to be a massive myocardial infarction. The investigator did not feel the events were related to study therapy.

10. Protocol/Study No. 006-067, AN 5310: This 73-year-old female with hypertension and a history of thyroidectomy and asthma received study infusion of heparin until Day 4. The patient was discharged on Day 5 but was readmitted on Day 10 for lightheadedness, leg swelling, and shortness of breath. She was found to have a large hematoma in the right groin catheterization site. A pulmonary embolism was suspected and was initially treated with heparin. The heparin was stopped because of a stool positive for occult blood. An inferior vena caval filter was inserted. A ventilation-perfusion scan was remarkable only for bronchospasms. On Day 15, the patient's condition worsened with shortness of breath and respiratory failure and she was intubated but continued to be hypoxemic. She developed bleeding from the gums and mouth and became bradycardiac, then asystolic. Resuscitative efforts were unsuccessful and she went into electromechanical dissociation and died on Day 15. The investigator felt that the death was due to a cardiopulmonary embolus and that none of the events was related to study therapy.

11. Protocol/Study No. 006-044, AN 6126: This 59-year-old male with bradycardia, premature ventricular contractions, and history of myocardial infarction, CABG, and resection of left ventricular aneurysm received prestudy open-label heparin followed by study infusion of heparin until Day 5. The clinical course during study infusion was uneventful. Angiography revealed severe coronary and graft disease. On Day 16, the patient underwent elective CABG and died intraoperatively. The cause of death was felt to be left ventricular dysfunction. The investigator felt that none of the events was related to study therapy.

12. Protocol/Study No. 006-044, AN 6155: This 72-year-old female with hypertension, diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, and hypothyroidism received prestudy open-label heparin followed by study infusion of heparin until Day 3. On Day 12, CABG was complicated by aortic dissection and uncontrollable bleeding culminating in death. The investigator felt that none of the events was related to study therapy.

13. Protocol/Study No. 006-059, AN 6326: This 72-year-old female was with hypertension, diabetes, and atherosclerosis was randomized with a non-Q-wave myocardial infarction received prestudy open-label heparin, but never received the study infusion of heparin because of difficult venous access. Subsequently, open-label heparin was initiated and given over 4 days. One day after cessation of heparin, the patient experienced severe ischemia, associated with sinus tachycardia, left bundle branch block and transient ST elevation. There were no enzyme elevations. The patient continued to have severe ischemia, developed cardiogenic shock on Day 6 and died on Day 7. The investigator felt the cardiogenic shock and death were not related to study therapy.

14. Protocol/Study No. 006-042, AN 6354: This 75-year-old female smoker with chronic renal failure and a history of arrhythmia, myocardial infarction and heart failure received prestndy open-label heparin followed by study infusion of heparin until Day 4. On Day 3, the patient was noted to have white cells in the urine, but was asymptomatic and afebrile. Angiography revealed severe left anterior descending coronary artery disease and on Day 4, she underwent PTCA. Because of significantly increased blood pressure, an intra-aortic balloon pump was installed on Day 4 and then removed on Day 5. Urine and blood cultures were positive for E. coli indicating bacteriuria (Day 8) and sepsis (Day 10), but the patient subsequently stabilized. On Day 19, the patient acutely developed respiratory distress and died of presumed pulmonary edema from a probable myocardial infarction. No autopsy was done. The investigator felt that the events were not related to study drug.

14.0.1 Death Narratives from PRISM-PLUS (protocol #006) (cont)

Heparin Group

15. Protocol/Study No. 006-043, AN 6366: This 81-year-old male with diabetes mellitus, dyspnea, nocturia, and remote history of syncope received prestudy open-label heparin followed by heparin infusion until Day 4. On Day 7, the patient began to have recurrent episodes of chest pain, diagnosed as a transmural myocardial infarction. The patient continued to have recurring chest pain and on Day 9 experienced ventricular tachycardia and cardiopulmonary arrest, and died. The investigator felt that none of the events was related to study therapy.

16. Protocol/Study No. 006-043, AN 6676: This 85-year-old male with peripheral vascular disease, left hemiblock, and history of myocardial infarction and CVA received study infusion of heparin until Day 4. On Day 14, angiography revealed triple-vessel disease and a PTCA was performed on Day 18. After the procedure, the patient developed hemodynamic instability progressing to hypovolemic shock, electromechanical dissociation, and death on Day 18. Based on autopsy, the cause of death was reported as hypovolemic shock from a left retroperitoneal hematoma following PTCA. The investigator felt that the none of the events was related to the study therapy.

17. Protocol/Study No. 006-050, AN 6696: This 92-year-old male with chronic renal insufficiency and carotid artery disease received prestudy open-label heparin followed by study infusion of heparin until Day 4. On the same day as study drug cessation, the patient suffered a new myocardial infarction complicated on Day 5 by pulmonary edema, cardiogenic shock, and worsening of renal insufficiency. Coronary angiography was deferred due to the unstable condition. On Day 8, the patient experienced more chest pain and life-threatening atria1 fibrillation. On Day 23, the patient died of cardiogenic shock secondary to the myocardial infarction and pulmonary edema. The investigator felt that none of the events was related to study therapy.

18. Protocol/Study No. 006-041, AN 6718: This 89-year-old male with heart failure, renal failure, and history of myocardial infarction received prestudy open-label heparin and was randomized to study infusion of heparin. Study drug was stopped prematurely on Day 2 for hematuria (not felt to be serious). On Day 3, the patient developed chest pain, worsening hypotension, and cardiogenic shock. There was ECG evidence of extension of an anterior myocardial infarction. The patient was treated conservatively and died on Day 3. The investigator felt that there was no relationship between these events and study therapy.

19. Protocol/Study No. 006-060, AN 6728: This 73-year-old male with hypertension, anemia, peripheral vascular disease, pulmonary venous hypertension, left atria1 hypertrophy, left ventricular hypertrophy, and history of myocardial infarction received prestudy open-label heparin followed by study infusion of heparin. On Day 4, following completion of study drugs, angiography was complicated by angina accompanied by severe hypotension with ECG ischemia. This progressed to cardiac arrest and the patient died on Day 4. The investigator felt that the cardiac arrest was not related to study therapy.

20. **Protocol/Study** No. 006-044, AN 6747: This 51-year-old male with hypertension, dyspnea, rales, diabetes mellitus, hypercholesterolemia and history of myocardial infarction and alcoholism received study infusion of heparin. On Day 4, study drugs were completed and the patient was discharged. Thirty-day follow-up information from the wife revealed that the patient died on Day 14 of a sudden cardiac arrest presumed to be a myocardial infarction, The investigator felt there was no relationship between study therapy and the death.

21. **Protocol/Study** No. 006-033, AN 6771: This 70-year-old male with hypertension and hypothyroidism received study infusion of heparin. On Day 3, following completion of study drugs, angiography revealed severe triple-vessel disease and the patient was scheduled for CABG. On Day 11, recurrent chest pain progressed to hypotension and cardiogenic shock (Day 12) with electromechanical dissociation. The patient died on Day 13. The investigator felt that there was no relationship between these events and study therapy.

22. Protocol/Study No. 006-044, AN 6818: This 75-year-old female with coronary artery disease and hypertension received study infusion of heparin. Following completion of study drug on Day 4, open-label heparin was initiated. On Day 9, angiography and PTCA were performed following which the patient developed an acute occlusion of the right coronary artery with an inferior-wall myocardial infarction, Emergency bypass surgery was performed on Day 9 and the postoperative course was complicated by thrombocytopenia with a platelet count nadir of $53 \times 10^9$ /L on Day 13. The platelet count improved to $122 \times 10^9$ /L by Day 16 and the patient was discharged on Day 18. The patient was readmitted on Day 21 for a pulmonary embolism complicated by thrombocytopenia. Following pulmonary angiography the patient deteriorated and suffered asystole and died on Day 21. Hematology consultation confirmed disseminated intravascular coagulation secondary to the pulmonary embolism. The investigator felt that none of the events was related to study therapy.

14.0.1 Death Narratives from PRISM-PLUS (protocol #006) (cont)

Heparin Group

23. Protocol/Study No. 006-042, AN 6861: This 68-year-old female smoker with hypertension, carotid stenosis, chronic obstructive pulmonary disease, hypothyroidism, and a history of diabetes mellitus and arrhythmia received prestudy open-label heparin followed by study infusion of heparin. Angiography on Day 5 revealed triple-vessel disease and the patient was scheduled for urgent CABG and study drugs were stopped. Prior to surgery, she experienced refractory ventricular fibrillation and subsequently died from a cardiac arrest shortly after surgery on Day 5. An autopsy confirmed a large M.I. dated at least 48 hours before death. The investigator felt that none of the events was related to study therapy.

24. Protocol/Study No. 006-034, AN 6981: This 75-year-old male smoker with chronic obstructive pulmonary disease, left ventricular dysfunction, diabetes mellitus, and history of myocardial infarction and hypertension received study therapy of heparin until Day 4. The patient was discharged on Day 10. On Day 18, the patient was readmitted with a non-Q-wave myocardial infarction complicated by pulmonary edema and atrial fibrillation. On Day 25, the patient died of pulmonary hemorrhage secondary to pulmonary artery rupture following inflation of the Swan-Ganz catheter balloon. The investigator felt that none of the events was related to study therapy.

25. Protocol/Study No. 006-044, AN 7079: This 78-year-old male ex-smoker with a history of myocardial infarction and cerebral vascular insufficiency was treated with open-label heparin prior to randomization to study infusion of heparin. At Hour 3, he developed anger with acute pulmonary edema and was subsequently intubated and study drug was stopped. Within an hour after study drug cessation he developed cardiogenic shock and atria1 fibrillation thereafter. Insertion of a subclavian catheter was complicated by traumatic puncture of the subclavian artery. Ventricular tachycardia with second degree AV block then developed, followed by anemia, elevated white blood cell count and cardiac enzymes, ventricular tachycardia, and finally asystole and death on Day 2. The investigator felt the events were not related to study therapy.

26. Protocol/Study No. 006-048, AN 7242: This 78-year-old female with a history of diabetes mellitus, hypertension, and coronary artery disease received prestudy open-label heparin followed by study infusion of heparin until Day 5. On Day 5, angiography revealed triple-vessel and left main coronary artery disease with good left ventricular function. Emergent CABG was followed by severely low cardiac output and the patient died on Day 5. The investigator felt that none of the events was related to study therapy.

27. Protocol/Study No. 006-048, AN 7248: This 77-year-old male with a history of myocardial infarction received open-label heparin prior to randomization to heparin study infusion. On Day 3, he suffered a myocardial infarction and developed cardiogenic shock. Study drug was stopped and an intra-aortic balloon pump, fibrinolysis, PTCA, and mechanical ventilation were implemented. The patient died of the myocardial infarction and cardiogenic shock on Day 4. The investigator felt the myocardial infarction and cardiogenic shock were not related to study therapy.

28. Protocol/Study No. 006-092, AN 7418: This 56-year-old male received prestudy open-label heparin followed by study infusion of heparin until Day 3. On Day 7, the patient developed renal insufficiency and pneumonia progressing to *Pseudomonas septicemia.* The patient became hemodynamically unstable and went into renal failure and died on Day 12. The investigator felt that none of the events was related to study therapy.

29. Protocol/Study No. 006-091, AN 7423: This 68-year-old male with diabetes mellitus, hypertension, and baseline elevated serum creatinine received prestudy open-label heparin followed by study infusion of heparin. On Day 2, study drug was discontinued for refractory ischemia with hemodynamic instability and the patient was taken to urgent angiography. On Day 5, the patient developed acute renal insufficiency, but continued to make urine. He was placed on open-label heparin for a mechanical prosthetic valve, but on Day 7 developed an upper extremity arterial occlusion treated with arterial surgery and urokinase. On Day 8, respiratory failure developed requiring ventilator support. On Day 9, he developed metabolic encephalopathy. He continued to deteriorate and on Day 13 developed circulatory shock and died on Day 14. The investigator felt that none of the events was related to study therapy.

30. Protocol/Study No. 006-093, AN 7457: This 79-year-old female with myocardial infarction, hypertension, and diabetes mellitus received prestudy open-label heparin followed by study infusion of heparin for 3 days. On Day 12, the patient developed pneumonia and respiratory insufficiency requiring artificial ventilation. The patient deteriorated and died on Day 22 due to respiratory insufficiency. The investigator felt that none of the events was related to study therapy.

31. Protocol/Study No. 006-094, AN 7613: This 68-year-old female with hypothyroidism received study infusion of heparin until Day 4. On Day 7, the patient undetwent PTCA and stent placement complicated by dissection of the coronary artery and death on Day 7. The investigator felt that none of the events was related to study therapy.

14.0.1 Death Narratives from PRISM-PLUS (protocol #006) (cont)

Heparin Group

32. Protocol/Study No. 006-089, AN 7631: This 46-year-old male with a history of myocardial infarction received study infusion of heparin. On Day 3, angiography was complicated by the development of cardiogenic shock and the study therapy was discontinued. Resuscitative efforts were unsuccessful and the patient died on Day 3. The investigator felt that none of the events was related to study therapy.

33. Protocol/Study No. 006-095, AN 7638: This 74-year-old male with diabetes mellitus and history of CABG and myocardial infarction received prestudy open-label heparin followed by study infusion of heparin until Day 5. On Day 8, the patient underwent CABG with the development of post operative hemodynamic instability and electrocardiographic ST segment elevation. On Day 9, the patient developed *Serratia* sepsis. On Day 12, the patient developed cardiogenic shock. The patient died on Day 13 from the cardiogenic shock. The investigator felt that none of the events was related to study therapy.

34. Protocol/Study No. 006-094, AN 7742: This 60-year-old male with a history of myocardial infarction and diabetes mellitus received prestudy open-label heparin followed by study infusion of heparin. On Day 2, the patient experienced cardiopulmonary arrest and study therapy was discontinued. Reanimation efforts were unsuccessful and the patient died on Day 2. The investigator felt that none of the events was related to study therapy.

35. Protocol/Study No. 006-084, AN 7804: This 75-year-old male with heart failure on admission and pulmonary edema with a history of myocardial infarction received prestudy open-label heparin followed by study infusion of heparin. The study infusion was discontinued prematurely on Day 1 due to re-emergence of heart failure. The patient subsequently improved and was scheduled for discharge on Day 5. Prior to leaving the hospital he experienced a sudden onset of chest pain and collapsed and was found to be in ventricular fibrillation. Resuscitation was unsuccessful and the patient died on Day 5. The ventricular fibrillation was believed to be precipitated by ischemia. The investigator felt that *none* of the events was related to study therapy.

36. Protocol/Study No. 006-108, AN 7852 : This 80-year-old female with non-Q-wave myocardial infarction, hypertension, and bronchitis, received study infusion of heparin until Day 5. On Day 6, she experienced cardiogenic shock and respiratory arrest and developed worsening bronchitis. On Day 7, decreased left ventricular function was confirmed by echocardiogram. On Day 10, the patient suffered asystole, cardiac arrest, and died. The investigator felt that none of the events was related to study therapy.

**8.1.1.1e** Deaths from the PRISM trial (protocol **#011)**

Through 30 days of follow-up, 96 subject deaths were reported for protocol #011 (A Randomized, Parallel, Double-Blind Study to Investigate the Safety and Clinical Efficacy of Tirofiban vs Heparin in Patients with Unstable Angina/Non-Q-Wave Myocardial Infarction. PRISM).

Table 8.1. 1.1e. I Deaths in the PRISM trial"

| Time of Follow-up | Tirofiban n=1616 | Heparin n=1616 | Total n=3232 |
|---|---|---|---|
| 48 hours | 6 (0.4%) | 4 (0.2%) | 10 (0.3%) |
| 7 days | 16 (1.0%) | 25 (1.6%) | 41 (1.3%) |
| 30 days | 37 (2.3%) | 59 (3.6%) | 96 (3.0%) |
| 30 days plus[b] | 40 (2.5%) | 62 (3.8%) | 102 (6.3%) |

a. Data from NDA volume 1.48, reference 9, tables 20-27.
b. Includes six subjects subjects who were submitted as SAEs but who died beyond the 30 days.

Narratives of circumstances leading to deaths are provided below for the 96 deaths (37 tirofiban and 59 heparin) that occurred during the study drug infusion period and up to Day 30 after randomization. Also included are six deaths that occurred outside the 30 day window but were included in the SAEs (3 deaths in each group).

Tirofiban Group

1. Protocol/Study No. 011-021, AN 1071: A 73-year-old female was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion without incident. On Study Day 4, the patient developed a cough and fever. A chest X-ray revealed pneumonia. Subsequently, she developed respiratory failure and respiratory arrest, The patient died due to respiratory failure as a complication of pneumonia on Day 8. The investigator felt that there was no relationship between these events and study therapy.

2. Protocol/Study No. 011-132, AN 1341 A 69-year-old female with a history of transient ischemic attack (TIA), cerebrovascular accident (CVA), myocardial infarction, and congestive heart failure was randomized to receive tirofiban. The study drug infusion was discontinued due to the patient withdrawing consent on Day 2. Later that day the patient began to experience respiratory failure. Pneumonia was diagnosed on Day 7. The patient subsequently developed severe hypotension and died 2 weeks later on Day 2 1. The probable cause of death was listed as respiratory failure. The investigator felt that there was no relationship between these events and study therapy.

3. Protocol/Study No. 011-032, AN 1349: An 89-year-old female with a history of ruptured cerebral hemorrhage was randomized to receive tirofiban. The patient discontinued the study drug infusion after 22 hours due to meeting an endpoint, refractory ischemia. The patient continued to receive maximal medical therapy after being considered to be a poor surgical candidate. On Day 8, a chest X-ray revealed pulmonary edema. The patient then developed new left bundle branch block followed by 2:1 heart block, and then asystole. Efforts to resuscitate the patient were unsuccessful and she died later that same day. The investigator felt that there was no relationship between these events and study therapy.

4. **Protocol/Study** No. 011-058, AN 1661: A 63-year-old male with a history of chronic obstructive pulmonary disease (COPD) was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion without incident. The patient was then transferred to an extended care facility. While at this facility, the patient developed pneumonia and a worsening of his COPD on Study Day 30. He was subsequently transferred to another hospital where the patient's pulmonary condition deteriorated further and he died on Study Day 3 1. The cause of death was identified as respiratory failure due to *worsening* COPD. The investigator felt that there was no relationship between these events and study therapy.

5. Protocol/Study No. 011-021, AN 1724: A 72-year-old male was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion without incident. On Study Day 5 the patient underwent cardiac catheterization which revealed severe triple-vessel coronary artery disease (CAD). He subsequently underwent a coronary artery bypass graft (CABG) procedure on Study Day 6 and never awoke postoperatively. An electroencephalogram revealed a coma and a CT scan revealed bi-hemispheric infarctions and left cerebellar infarction. It was determined that the patient suffered a large air embolus stroke during open heart surgery. Life support was withdrawn at the family's request and, on Study Day 15, the patient died. The investigator felt that there was no relationship between these events and study therapy.

**8.1.1.1e** Death Narratives from the PRISM trial (protocol #011-) (cont)

Tirofiban Group

6. Protocol/Study No. 011-093, AN 1756: A 70-year-old female with a history of myocardial infarction was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion. The patient remained in the hospital for a scheduled CABG procedure. On Day 7, the patient had a bowel movement and thereafter complained of chest pain. She developed hypotension, cardiac arrhythmia, and ultimately went into cardiac arrest. She was unsuccessfully resuscitated and died later that same day. The investigator felt that there was no relationship between these events and study therapy.

7. Protocol/Study No. 011-008, AN 2187: An 86-year-old female with a history of myocardial infarction was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion. Later on Day 3, an ECG revealed new ischemic changes. At this time the patient was thought to have developed an acute Q-wave myocardial infarction. Systolic blood pressure continued to drop and the patient went into cardiac arrest. The patient was successfully resuscitated. The patient was continually monitored throughout the night; however, the patient's family requested no further measures be taken. On the morning of Day 4, the patient went into asystole and died. The investigator felt that there was no relationship between these events and study therapy.

8. Protocol/Study No. 011-089, AN 2417: A 66-year-old male with a history of COPD, multiple CABG procedures, percutaneous transluminal coronary angioplasty (PTCA) procedures, and two myocardial infarctions was to be randomized to tirofiban; however, due to the patient's rapid clinical course the study drug was never initiated. The patient's creatine phosphokinase (CPK) values continued to increase from 3596 U/L to 5445 U/L from his admitting M.I. On Day 3, the patient became hypotensive and went into cardiogenic shock. An intra-aortic balloon pump was inserted and his blood urea nitrogen (BUN) and serum creatinine were continually monitored. The patient subsequently requested a "DNR" order and expired approximately 1 week later. The investigator felt that there was definitely no relationship between these events and study therapy.

9. Protocol/Study No. 011-023, AN 2518: A 63-year-old female was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion without incident. The patient underwent a cardiac catheterization procedure that revealed triple-vessel disease. A CABG was performed on Day 7, during that the patient suffered a massive extension of a myocardial infarction. She also experienced bleeding diathesis and multiple organ failure. The patient died the next day. The investigator felt that there was no relationship between these events and study therapy.

10. Protocol/Study No. 011-082, AN 2849: A 67-year-old female was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion uneventfully and was subsequently discharged. On Day 14, the patient collapsed after complaining of severe and sudden chest pain. Upon admission to a peripheral hospital, she was in cardiogenic shock. Resuscitation attempts were unsuccessful. The cause of death was reported as cardiogenic shock, probable reinfarction. The investigator felt that there was no relationship between the patient's experience and study therapy.

11. Protocol/Study No. 011-100, AN 3000: A 68-year-old male was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion uneventfully and was subsequently transferred to another facility for angiography testing that confirmed the need for a bypass procedure. On Day 18, he underwent successful bypass surgery and left the operating room in stable condition. Later that day, the patient experienced severe hypotension and was never stabilized. The patient then developed cardiogenic shock and underwent a second bypass. The patient died of cardiogenic shock in the operating room. The investigator felt that there was no relationship between these events and study therapy.

12. Protocol/Study No. 011-102, AN 3016: An 84-year-old male with a history of TIA and myocardial infarction was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion. On Day 5, the patient underwent a scheduled coronary angiogram procedure during which he went into cardiogenic shock. An intra-aortic balloon pump was inserted. The patient then underwent another emergency cardiac bypass surgery from which he did not recover. The patient died on Day 6. The investigator felt that there was no relationship between these events and study therapy.

13. Protocol/Study No. 011-062, AN 3076: A 70-year-old male was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion without incident. The patient underwent a scheduled coronary angiography on Day 4. When the contrast media was introduced the patient suddenly experienced ventricular fibrillation and died in the hospital angiography room. The investigator felt that there was no relationship between these events and study therapy.

14. Protocol/Study No. 011-061, AN 3098: A 71-year-old female was randomized to receive tirofiban and completed the 48-hour study drug infusion. On Day 10, the patient had an episode of syncope. The patient was discharged home on Day 1 I. The next morning the patient was found dead. The cause of death was thought to be sudden cardiac death. The investigator felt that there was no relationship between these events and study therapy.

**8.1.1.1e** Death Narratives from the PRISM trial (protocol **#011-) (cont)**

Tiroliban Group

**15. Protocol/Study** No. **011-129,** AN 3134: A 74-year-old female was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion. On Day 13 the patient was transferred to another facility for a scheduled CABG procedure. During the postoperative period she experienced a myocardial infarction. The patient then went into cardiogenic shock and died on Day 17. The investigator felt that there was no relationship between these events and study therapy.

16. Protocol/Study No. 011-097, AN 3224: A 65-year-old female with a history of myocardial infarction was randomized to receive tirofiban. On Day 2, signs of mild heart failure were noted but the study drug infusion was continued for the full 48-hour duration. The patient developed severe pulmonary edema the next day. An emergency bypass surgery was scheduled based on the patient condition and the results of an angiography. Due to technical difficulties during the procedure, the patient sustained failure of the right ventricle and subsequently died on Day 3. The primary cause of death was most probably due to biventricular heart failure that occurred following right ventricular laceration traumatically caused by the surgeon in opening the chest wall. The investigator felt that there was no relationship between these events and study therapy.

17. Protocol/Study No. 011-065, AN 3286: A 52-year-old male was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion. On Day 9 the patient's CPK results were elevated and rhabdomyolysis was diagnosed. The patient also developed acute renal insufftciency. On Day 14 he developed cardiogenic shock, therapy with adrenaline, dobutamine, and dopamine was started. The patient died on Day 19. The investigator felt that there was no relationship between these events and study therapy.

18. Protocol/Study No. 011-079, AN 3502: A 68-year-old male with a history of heart failure was randomized to receive tirofiban. The patient completed the 48-hour drug infusion without incident. On Day 16, a CABG procedure was performed. During the procedure a perioperative myocardial infarction occurred and the patient developed worsening heart failure and hypotension. Two days later he died. The investigator felt that there was no relationship between these events and study therapy.

19. Protocol/Study No. 011-065, AN 3527: A 45-year-old female was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion uneventfully. On Day 4 the patient experienced worsening angina and an angiogram was performed showing angioplasty restenosis in the right coronary and a proximal lesion of 90% of the circumflex. On Study Day 16 the patient underwent revascularization. The patient experienced an infarction perioperatively and died. The investigator felt that there was no relationship between these events and study therapy.

20. Protocol/Study No. 011-061, AN 3620: A 73-year-old male with a history of abdominal aortic aneurysm was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion and 5 days later underwent a CABG procedure on Day 8. There were postsurgery complications. They had difficulty getting the patient off bypass and he had to be ventilated. The patient subsequently went into a coma on Day 11. Two days later he developed pseudomonas septicemia. A CT brain scan was performed on Day 16 that showed no hemorrhage, no hydrocephalus and no subdural hemorrhage. The scan did show a CVA. A neurologist assessment said that the persistent coma suggested sustained severe hypo-ischemic encephalopathy. On Day 18 ventilation was removed and the patient died. The investigator felt that there was no relationship between these events and study therapy.

21. **Protocol/Study** No. 011-076, AN 3697: A 69-year-old female was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion. A cardiac catheterization procedure revealed normal coronary arteries and tight aortic stenosis. The patient was discharged in good condition. During the 30-day follow-up the investigator was informed that on Day 30, the patient had felt extremely well and had resumed all her regular activities. She went to the toilet and there she was found dead. No cause of death was identified. The investigator felt that there was no relationship between these events and study therapy.

22. Protocol/Study No. 011-123, AN 3888: A 68-year-old female with a history of myocardial infarction was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion and on Day 9 underwent a CABG procedure. Following the surgery the patient experienced an acute myocardial infarction, cardiogenic shock, myelopathy, and heart failure. She also experienced CVA and respiratory insufficiency. Approximately 2 weeks later the patient's condition worsened with the addition of cardiogenic shock, renal insufftciency, and pneumonia. On Day 40 the patient died. The cause of death was renal failure, respiratory insufficiency, and pneumonia. The investigator felt that there was no relationship between these events and study therapy.

23. Protocol/Study No. 011-085, AN 3905: A 42-year-old male was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion. On Day 9 the patient died. The cause of death was cerebral edema and myocardial infarction. The patient died at home and the attending physician gave the result of death as acute myocardial infarction from the previous history. The investigator felt that there was no relationship between these events and study therapy.

**8.1.1.1e** Death Narratives from the PRISM trial (protocol #011-) (cont)

**Tirofiban** Group

24. Protocol/Study No, 011-063, AN 3929: A 69-year-old male with a history of stroke, peripheral artery disease, and myocardial infarction was randomized to receive tirofiban. On Day 2 the patient experienced a myocardial infarction. The study drug infusion was discontinued due to the patient meeting this endpoint. During an angiography procedure, the catheter could not be advanced to the aorta because of severe arteria iliaca stenosis, left and right. On Day 7 the patient was transferred to the genera1 ward and experienced recurrent angina. An ECG revealed a new myocardial infarction. The patient died later that day. The investigator felt that there was no relationship between these events and study therapy.

25. **Protocol/Study** No. 011-070, AN 4398: A 66-year-old male with a history of myocardial infarction, peripheral vascular disease (PVD), triple-vessel disease, heart failure, and hypertension was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion. On Day 10, the patient underwent a CABG procedure. Two days later the patient developed pulmonary edema. The patient was treated with furosemide and recovered. On Day 14 the patient had a fever and there was pus at the CABG wound site. The patient was subsequently treated with antibiotics. During this period of time the patient's laboratory test values fluctuated in and out of normal range. The patient then began to develop hypoxia and probably began to develop acute respiratory distress syndrome. The patient's renal function deteriorated and on Day 28 hemodialysis began. Three days later sternal closure was attempted. Following this, the patient became more hypoxic, his renal failure worsened and he became acidotic. The patient died the next day. The investigator felt that there was no relationship between these events and study therapy.

26. Protocol/Study No. 011-140, AN 4403: A 76-year-old male with a history of heart failure was randomized to receive tirofiban. On Day 2 the patient went into severe heart failure. Due to the severity of the patient's condition the study drug infusion was prematurely discontinued on Day 3. Approximately 4 hours later the patient died. The investigator felt that there was no relationship between the patient's experience and study therapy.

27. Protocol/Study No. 011-140, AN 4418: A 68-year-old female with a history of hypertension and ischemic heart disease was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion. On Day 5 an ECG had shown ST depression and subsequent cardiac enzymes were elevated consistent with a myocardial infarction. The patient died later that same day. The cause of death was cardiac arrest. The investigator felt that there was no relationship between these events and study therapy.

28. Protocol/Study No. 011-065, AN 4940: A 75-year-old male was randomized to receive tirofiban. The patient experienced cardiac arrest and electromechanical dissociation on Day 2 that prompted the discontinuation of study drug therapy. Later that same day the patient died. The investigator felt that there was no relationship between these events and study therapy.

29. Protocol/Study No. 011-079, AN 5032: A 66-year-old male was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion. A CABG procedure was performed on Day 8. On that same date, the patient experienced postoperative bleeding, metabolic acidosis, worsening heart failure, electromechanical dissociation and died. The causes of death were worsening heart failure and electromechanical dissociation. The investigator felt that there was no relationship between these events and study therapy.

30. Protocol/Study No. 011-125, AN 5061: A 69-year-old female was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion uneventfully and was subsequently discharged home. The patient experienced a myocardial infarction and pneumonia and was rehospitalized. The patient died on Day 7. The patient had also experienced asystole at the time of death. The causes of death were myocardial infarction, pneumonia, and asystole. The investigator felt that there was no relationship between these events and study therapy.

31. Protocol/Study No. 011-162, AN 5187: A 69-year-old male was randomized to receive tirofiban. The patient's condition continued to worsen after only receiving study drug for 6 hours. Two hours after study drug discontinuation the primary investigator decided to treat the patient with thrombolytic therapy. The patient experienced hemodynamic instability/cardiogenic shock, which possibly caused the patient's death on Day 2. The investigator felt that there was no relationship between these events and study therapy.

32. Protocol/Study No. 011-114, AN 5597: A 58-year-old male was randomized to receive tirofiban. After receiving the study drug therapy for approximately 6 hours, the investigator discontinued the infusion due to the patient meeting an endpoint of myocardial infarction. The investigator decided to perform an urgent PTCA based on the angiography results and the presence of Q-waves prior to study drug discontinuation. The patient developed cardiomyopathy and an intra-aortic balloon pump was installed. A CABG was promptly performed; however, during the procedure air got into the right coronary artery (RCA) with a right ventricular asystole as a result. After this, the patient developed cardiac tamponade with right ventricular heart failure and cardiogenic shock. The patient subsequently died from cardiac tamponade, heart failure, and cardiogenic shock on Day 2. The investigator felt that there was no relationship between these events and study therapy.

**8.1.1.1e** Death Narratives from the **PRISM** trial (protocol **#011-) (cont)**

Tirofiban Group

33. Protocol/Study No. 011-155, AN 6552: A 61-year-old male was randomized to receive tirofiban. After receiving the study drug therapy for approximately 40 hours, the investigator discontinued the infusion due to the patient meeting an endpoint of myocardial infarction. Streptokinase was administered on the basis of a presumed infarct. The patient continued to experience chest pain. During the night of Day 3 the patient became profoundly hypotensive. At about the same time the patient passed a large quantity of melena. Open-label heparin was stopped. Haemacel 500 mL was infused rapidly followed by four units of PRBCs. The patient became increasingly distressed around midnight and became bradycardic with no cardiac output. Despite resuscitation attempts the patient died at 00:20 on Day 4. Preliminary results from a postmortem examination revealed findings of a recent myocardial infarction and a massive gastrointestinal hemorrhage filling both large and small bowel. No obvious bleeding site was identified. The investigator felt that there was no relationship between these events and study therapy.

34. Protocol/Study No. 011-172, AN 6784: A 43-year-old male was randomized to receive tirofiban. The patient was admitted into the study with evidence of a non-Q-wave myocardial infarction. During the study drug infusion the patient experienced chest pain at rest and became unresponsive. A few minutes later the patient experienced cardiac arrest. Resuscitation attempts failed and the patient died the morning of Day 2. The investigator felt that there was no relationship between these events and study therapy.

35. Protocol/Study No. 011-170, AN 6816: A 60-year-old male with a history of TIA and CABG was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion uneventfully. On Day 11 the patient underwent a CABG procedure. The patient went into cardiogenic shock after the procedure. An insertion of an intra-aortic balloon pump failed. The patient subsequently died on Day 12. The cause of death was cardiogenic shock secondary to ischemic heart disease. The investigator felt that there was no relationship between these events and study therapy.

36. Protocol/Study No. 011-168, AN 6923: An 80-year-old female with a history of CABG was randomized to receive tirofiban. During the study drug infusion the patient experienced asystolic cardiac arrest secondary to a myocardial infarction. The patient also experienced severe anoxic brain damage at this time. The patient underwent cardiopulmonary resuscitation including adrenaline, atropine, and intubation resulting in recovery of cardiac output, pulse, and blood pressure. Periarrest CPK was 999 U/L,. Study drug therapy was discontinued after stabilizing the patient the morning of Day 2. ECG evidence confirmed an acute anterior myocardial infarction. An hour later the patient's respiration was depressed and exhibiting Cheyne-Stokes pattern. Neurologically, there was no eye opening, no response to pain, and her pupils were mid-sized and fixed. Cardiovascularly, her blood pressure was unstable and required intermittent boluses of adrenaline for support. In the early morning of Day 3 the patient died. The investigator stated that the probable cause of death was cerebral hypoxia, secondary to asystole arrest and acute myocardial infarction, which lead to irreversible neurological deficit. The investigator felt that there was no relationship between these events and study therapy.

37. Protocol/Study No. 011-168, AN 6987: A 66-year-old female was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion without incident. On Day 14, the patient underwent a CABG procedure of the four vessels. Three days later she experienced respiratory collapse and then severe renal insufficiency. Three days later the patient died. A postmortem found the cause of death to be myocardial infarction due at CABG. The investigator felt that there was no relationship between these events and study therapy.

38. Protocol/Study No. 011-072, AN 7005: A 72-year-old male with a history of triple-vessel disease and myocardial infarction was randomized to receive tirofiban. The patient completed the 48-hour study drug infusion. The patient continued to complain of chest pain and on Day 10 the patient underwent a CABG procedure at another facility. The patient initially made a good recovery; however, 2 days later the patient complained of abdominal pain and distention. The patient continued to have abdominal pain; he became breathless and cyanosed; his urine output was poor and results of blood tests showed he had developed metabolic acidosis. The patient was diagnosed with intestinal vascular insufficiency. Despite measures to correct the acidosis and to provide inotropic support he died on Day 13. The investigator felt that there was no relationship between these events and study therapy.

39. Protocol/Study No. 011-061, AN 7550: A 78-year-old female was randomized to receive tirofiban. Approximately 6 hours after the initiation of the study drug infusion, the patient had a myocardial infarction with associated ECG changes and chest pain. The patient experienced shortness of breath and cardiogenic shock 2 hours later. The patient was intubated, ventilated, and given CPR. Study drug therapy was not interrupted. On Study Day 4 the patient died. The cause of death was cardiac arrest. The investigator felt that there was no relationship between these events and study therapy.

**8.1.1.1e** Death Narratives from the PRISM trial (protocol **#011-) (cont)**

**Tirofiban** Group

40. ProtocoUStudy No. 011-167, AN 7859: A 41-year-old female was randomized to receive tirofiban. The patient's study drug infusion was prematurely discontinued due to nausea and vomiting brought on by the patient's apprehension over her physical condition. The patient was subsequently discharged from the hospital. The investigator site tried contacting the patient to record her 30-day status at which time the patient's mother informed the site that she had died. On Study Day 8, the patient collapsed to the floor and was unable to get up. The patient was diagnosed with a CVA, although the study site did not know if it was embolic or hemorrhagic. The patient was placed on a respirator and died 2 days later, while still on the respirator. The cause of death was reported as CVA. The investigator felt that there was no relationship between these events and study therapy.

Heparin Group

1. ProtocoUStudy No. 011-021, AN 1232: A 66-year-old female was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident and was subsequently discharged. On Study Day 19 she was readmitted with a diagnosis of pulmonary embolus. The embolus resolved; however, the patient developed progressive congestive heart failure (CL-IF) and died of heart failure on Study Day 43. The investigator felt that there was no relationship between these events and study therapy.

2. Protocol/Study No. 011-092, AN 1320

A 73-year-old male was randomized into the study but did not receive any study drug. Prior to the patient receiving any study drug, his ECG changes indicated an acute myocardial infarction. He was subsequently transferred to another facility for a PTCA procedure. During this hospitalization the patient died (Day 13). The death was attributed to an intracranial hemorrhage and dissecting aneurysm of the ascending aorta. The investigator felt that there was no relationship between these events and study therapy.

3. ProtocoUStudy No. 011-054, AN 1701: A 74-year-old male with a history of CAD was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident. Results of a cardiac catheterization done on Study Day 4 revealed severe native CAD and one of three grafts was completely occluded. He was deemed inoperable. Approximately 12 hours later he died due to severe CAD. The investigator felt that there was no relationship between the patient's experience and study therapy.

4. ProtocoUStudy No. 011-089, AN 2390: A 78-year-old male was randomized to receive heparin. During the study drug infusion the patient's laboratory results revealed an elevated CPK of 1203 and approximately 5 hours later a serum CPK of 1686. Subsequently the study drug infusion was prematurely terminated due to an elevated serum creatinine result of 5.0. The patient continued to experience chest pain and his CPK results continued to increase from an evolving myocardial infarction. On Study Day 3 the patient died. The investigator felt that there was no relationship between these events and study therapy.

5. ProtocoUStudy No. 011-089, AN 2391: A 70-year-old female with a history of COPD and CHF was randomized to receive heparin. The patient completed the 48-hour study drug infusion. The patient's hospitalization was prolonged due to the patient's evolving myocardial infarction. Subsequently, the patient developed worsening COPD. The patient's BUN/Serum Creatinine values continued to worsen and on Day 7 the patient died. The investigator felt that there was no relationship between these events and study therapy.

6. ProtocoUStudy No. 011-092, AN 2467: A 71-year-old female with a history of severe multi-vessel coronary artery disease and myocardial infarction was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident. On Day 15, the patient underwent two-vessel CABG and aortic valve replacement. Later that day she developed mediastinal bleeding. The patient was transferred to the operating room for exploration that revealed cardiac tarnponade. The patient then went into cardiogenic shock and subsequently died. The investigator felt that there was no relationship between these events and study therapy.

7. Protocol/Study No. 011-021, AN 2504: A 91-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident and was subsequently discharged. On Study Day 17 the patient died at home. The cause of death was reported to be myocardial infarction. The investigator felt that there was no relationship between the patient's experience and study therapy.

8. ProtocoUStudy No. 011-085, AN 2809: A 66-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident. He was transferred to another facility for a scheduled CABG procedure. On Day 17 he experienced renal insufficiency and then he experienced a perioperative myocardial infarction on Day 24. The patient was medically treated and on Day 24 a CT scan of the brain revealed a CVA. That same day the patient died. The investigator felt that there was no relationship between these events and study therapy.

**8.1.1.1e** Death Narratives from the PRISM trial (protocol **#011-) (cont)**

Heparin Group

9. ProtocoUStudy No. 011-079, AN 2831: A 62-year-old male with a history of heart failure was randomized to receive heparin. After 12 hours of therapy the study drug infusion was discontinued due to the patient meeting an endpoint, refractory ischemia. An IABP was promptly placed, causing an aortic dissection. On Day 2, the patient also developed worsening heart failure. The patient was scheduled to undergo a CABG procedure at another hospital. His prior angiography showed a proximal obstruction of three vessels. On Day 9, the patient died of worsening heart failure. The investigator felt that there was no relationship between these events and study therapy.

10. ProtocoUStudy No. 011-082, AN 2844: A 67-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion uneventfully except for an episode of chest pain the morning of Day 3. One and a quarter hours after completing the study drug infusion, the patient collapsed and had no pulse. Attempts of resuscitation were unsuccessful. Probable causes of death were identified as possible ventricular fibrillation and arrhythmia. The investigator felt that there was no relationship between these events and study therapy.

11. ProtocoUStudy No. 011-082, AN 2854: A 54-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion uneventfully and was subsequently discharged. During his admission the patient underwent an elective coronary angiogram that revealed triple-vessel disease with poor LV function. On Day 21 he developed severe retrostemal chest pain and was readmitted. Myocardial infarction was confirmed by ECG. The patient suddenly died the next day presumably from ventricular arrhythmia. The investigator felt that there was no relationship between these events and study therapy.

12. ProtocoUStudy No. 011-085, AN 2866: A 60-year-old female was randomized to receive heparin. The patient completed the 48-hour study drug infusion uneventfully and was subsequently transferred to another facility for a scheduled CABG procedure. The patient developed septicemia and renal insufficiency. The patient was treated medically with nystatin, tobramycin, and imipenem-cilastatin sodium. The patient died on Day 24. The investigator felt that there was no relationship between these events and study therapy.

13. ProtocoUStudy No. 011-061, AN 2876: A 78-year-old male was to be randomized to heparin; however, due to the patient's continuing chest pain and new ECG changes, the investigator decided to start the patient on thrombolytic therapy. While the patient's CPK results were increasing, confirming a large infarction, the patient also developed pulmonary edema. The next day the patient slipped into cardiogenic shock and continued to decline. The patient died 2 days later. The investigator felt that there was no relationship between these events and study therapy.

14. Protocol/Study No. 011-118, AN 2964: A 57-year-old male with a history of myocardial infarction and tuberculosis was randomized to heparin. The morning of Day 2, the patient's I.V. tubing became disconnected and the patient bled at the I.V. site. The patient received two units of PRBCs and study drug therapy was not reinitiated. On Day 3, the patient underwent an angiography followed with a PTCA procedure. Shortly after that the patient developed cardiogenic shock with pulmonary edema, ventricular fibrillation, and then died. The investigator felt that there was no relationship between these events and study therapy.

15. Protocol/Study No. 011-098, AN 3030: A 75-year-old male with a history of pulmonary emphysema was randomized to receive heparin. The patient completed the 48-hour study drug infusion; however, his condition worsened from baseline. He developed edema, bronchospasm, and cardiac arrhythmia. During the course of events the family requested that no intervention should be done. On Day 5 the patient experienced atria1 fibrillation and early the next day the patient died from cardiogenic shock. The investigator felt that there was no relationship between these events and study therapy.

16. ProtocoUStudy No. 011-061, AN 3091: An 89-year-old female was randomized to receive heparin. The patient completed the 48-hour study drug infusion. The patient then received open-label heparin therapy up to Day 11. On Day 18 the patient experienced a clinically large CVA. Nine days later the patient died. The investigator felt that there was no relationship between the patient's experience and study therapy.

17. ProtocoUStudy No. 011-066, AN 3102: An 83-year-old male with a history of myocardial infarction was randomized to heparin. The patient completed the 48-hour study drug infusion; however, the patient was diagnosed with pneumonia on the same day. The patient's pneumonia persisted. Pulmonary edema and continuous hypotension occurred on Day 5. The next day the patient experienced a myocardial infarction and subsequently died. The investigator felt that there was no relationship between the patient's experience and study therapy.

18. ProtocoUStudy No. 011-116, AN 3123: A 63-year-old male with a history of myocardial infarction was randomized to heparin. The patient completed the 48-hour study drug infusion uneventfully. He underwent a scheduled CABG procedure on Day 13. During surgery the patient experienced an acute myocardial infarction. Consequently, the patient suffered cardiogenic shock, pneumonia and septic shock. The patient never recovered and died on Day 22. The investigator felt that there was no relationship between the patient's experience and study therapy.

8.1.1.1e Death Narratives from the PRISM trial (protocol #011-) (cont)

Heparin Group

19. Protocol/Study No. 011-129, AN 3132: A 79-year-old female was randomized to receive heparin. The patient completed the 48-hour study drug infusion. On Day 16 the patient experienced an acute myocardial infarction and pulmonary edema and died the next day. The investigator felt that there was no relationship between the patient's experience and study therapy. WAES No. 95029 117.

20. Protocol/Study No. 011-065, AN 3277: A 71-year-old female was randomized to receive heparin. The patient completed the 48-hour study drug infusion. The patient developed pulmonary edema due to hemodynamic instability on Day 4. Inotropic agents, nitroglycerin, and dobutamine were started and the patient improved. On Day 15 the patient suddenly developed ventricular fibrillation, atrioventricular dissociation and died. The investigator felt that there was no relationship between the patient's experience and study therapy.

21. Protocol/Study No. 011-065, AN 3280: A 50-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion. On Day 5 an angiography was performed revealing triple-vessel disease and the bypass from the saphenous vein that was implanted from an earlier CABG. The patient presented suddenly with a loss of consciousness on Day 16 and a CT scan showed a hemorrhagic CVA. The patient died later that same day. The investigator felt that there was no relationship between the patient's experience and study therapy.

22. Protocol/Study No. 011-062, AN 3335: A 68-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion. On Day 3 an angiography revealed partial obstruction of the proximal left anterior descending artery, the proximal circumflex artery, and the vertical segment of the right coronary artery. The patient was placed in the coronary care unit and suddenly presented with acute pulmonary edema, electromechanical dissociation, cardiogenic shock and died. The investigator felt that there was no relationship between the patient's experience and study therapy.

23. Protocol/Study No. 011-044, AN 3353: A 53-year-old male with triple-vessel disease was randomized to receive heparin. The patient completed the 48-hour study drug infusion and subsequently underwent an angiography. On Day 6 he underwent a CABG procedure. The patient failed to regain consciousness postoperatively. A CT scan of the brain showed loss of gray/white interface of both cerebral hemispheres and minor effacement of the lateral ventricles, suggestive of bilateral cerebral ischemia. The patient was subsequently diagnosed with anoxic brain damage due to a perioperative myocardial infarction. Follow-up information revealed that the patient died on Day 55. The investigator felt that there was no relationship between the patient's experience and study therapy.

24. Protocol/Study No. 011-044, AN 3358: A 75-year-old female was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident and was subsequently discharged. On Study Day 18 the patient experienced syncope. After she regained consciousness, she experienced dizziness, middle ear disorder, tinnitus, and slight chest pain. During her rehospitalization she was found to be in biventricular failure. It was noted that she had apparently taken two tablets of chlordiazepoxide the previous night. An X-ray revealed a basilar skull fracture. On the morning of Day 30, she was found to be short of breath after going to the bathroom. Subsequently she experienced cardiac arrest. During resuscitation attempts a rhythm strip indicated ventricular fibrillation. The resuscitation was not successful and she died on Day 30. The investigator felt that there was no relationship between the patient's experience and study therapy.

25. Protocol/Study No. 011-065, AN 3524: A 67-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident and was subsequently discharged. On Study Day 15 the patient experienced an arrhythmia and died. The investigator felt that there was no relationship between the patient's experience and study therapy.

26. Protocol/Study No. 011-045, AN 3686: A 51-year-old male with triple-vessel disease and a history of myocardial infarction was randomized to receive heparin. The patient completed the 48-hour study drug infusion. On Day 12 the patient died. The cause of death was myocardial infarction and arrhythmia. The investigator felt that there was no relationship between the patient's experience and study therapy.

27. Protocol/Study No. 011-117, AN 3791: A 79-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident and was subsequently discharged. On Study Day 25 the patient experienced a myocardial infarction and was readmitted. Three days later the patient had a reinfarction and died. The investigator felt that there was no relationship between these events and study therapy.

28. Protocol/Study No. 011-065, AN 3893: A 61-year-old female was randomized to receive heparin. The study drug infusion was withdrawn 9 hours prior to completion due to the patient meeting an endpoint of myocardial infarction. An angiography was performed revealing a greater than 90% occlusion in the ostium of the left coronary artery. Urgent CABG was subsequently done. On Day 4 the patient experienced cardiac arrest and cardiogenic shock requiring inotropic support. The patient died 2 days later. The investigator felt that there was no relationship between these events and study therapy.

**8.1.1.1e** Death Narratives from the PRISM trial (protocol #011-) (cont)

Heparin Group

29. **Protocol/Study** No. 011-060, AN 4015: A 51-year-old male was randomized to receive heparin. The study drug infusion was not completed due to the patient meeting an endpoint, myocardial infarction. The patient died after experiencing cardiogenic shock and respiratory failure, approximately 2 hours after discontinuing the drug infusion on Day 3. The investigator felt that there was no relationship between these events and study therapy.

30. Protocol/Study No. 011-060, AN 4041: A 65-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion. On Day 9 the patient experienced a new episode of angina followed by an acute myocardial infarction. An angiography showed obstructive lesions in the coronary artery and bypass surgery was indicated. The procedure was performed on Day 11 and after that the patient never recovered consciousness. A CT scan was performed and disclosed the diagnosis of cerebral vascular accident, ischemic in multiple areas of the central nervous system, probably as a complication of the extracorporeal circulation used in surgery. The patient was considered to be in a chronic coma as a sequela of the CVA. On Day 71 the patient experienced respiratory failure and died the next day. The investigator felt that there was no relationship between these events and study therapy.

31. **Protocol/Study** No. 011-155, AN 4375: A 77-year-old female with a history of deep vein thrombosis and myocardial infarction was randomized to receive heparin. The patient completed the 48-hour study drug infusion. An angiography performed on Day 5 showed severe triple-vessel disease. The next day the patient had an angina1 attack at rest with ECG changes. She also experienced a myocardial infarction the same day. On Day 8 the patient had an emergency PTCA to LAD with stent placement. However, she continued to experience angina1 pain. The patient then developed acute renal insufficiency and pulmonary edema. On Day 11 the patient experienced another myocardial infarction and subsequently died. The investigator felt that there was no relationship between these events and study therapy.

32. ProtocoYStudy No. 011-072, AN 4425: A 77-year-old female was randomized to receive heparin. During the study drug infusion the patient felt a "heaviness" in her chest but was pain-free. An ECG showed T-wave inversion. The patient's serum CPK result was high at 1476 U/L in the morning of Day 2. By 17:45 that night the patient's CPK had risen to 2073 U/L, which indicated the patient experienced an anterior myocardial infarction. An ECG also showed T-wave inversion and she was found to be bradycardic. The next day the patient completed the 48-hour study drug infusion; however, she was still bradycardic and still had elevated CPK results. On Day 6 the patient was found pulseless but warm by a nurse. Resuscitation attempts failed and the patient was certified dead at 03:40. The investigator felt that there was no relationship between the patient's experience and study therapy.

33. Protocol/Study No. 011-123, AN 4661: An 82-year-old male with a history of hypertension, heart failure, gastritis, valvular heart disease, and myocardial infarction was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident. On Day 7 the patient died due to cardiogenic shock. The investigator felt that there was no relationship between the patient's experience and study therapy.

34. Protocol/Study No. 011-123, AN 4669: A 55-year-old male with a history of femoral/popliteal bypass and an aneurysm of the aorta was randomized to receive heparin. The patient completed the 48-hour study drug infusion. On Day 4 the patient experienced an acute myocardial infarction, pulmonary edema, asystole and died. The investigator felt that there was no relationship between the patient's experience and study therapy.

35. Protocol/Study No. 011-123, AN 4674: An 82-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident. On Study Day 9 the patient experienced a myocardial infarction and died. The investigator felt that there was no relationship between the patient's experience and study therapy.

36. Protocol/Study No. 011-151, AN 4802: A 56-year-old male with ischemic heart disease was randomized to receive heparin. The patient completed the 48-hour study drug infusion and was subsequently discharged. The patient had been well since discharge apart from one angina1 attack on Study Day 15 from which he recovered. However, the patient died the next day. The cause of death was thought due to sudden cardiac death secondary to ischemic heart disease. The investigator felt that there was no relationship between these events and study therapy.

37. Protocol/Study No. 011-125, AN 4884: A 74-year-old female with a history of heart failure was randomized to receive heparin. On Study Day 2 the patient died. The cause of death was cardiogenic shock. The investigator felt that there was no relationship between the patient's experience and study therapy.

38. **Protocol/Study** No. 011-127, AN 4902: A 71-year-old female was to be randomized to heparin; however, the patient met an exclusion criteria due to an earlier treatment with thrombolytics and never received study drug. The patient was readmitted after experiencing a cerebral infarction. The patient died 2 days later. The investigator felt that there was definitely no relationship between these events and study therapy.

8.1.1.1e Death Narratives from the PRISM trial (protocol #011-) (cont)

Heparin Group

39. Protocol/Study No. 011-127, AN 4905: A 77-year-old female with a history of asystole, hypertension, and heart failure was randomized to receive heparin. The patient completed the 48-hour study drug infusion. On Study Day 4 the patient died. The cause of death was asystole secondary to acute myocardial infarction. The investigator felt that there was no relationship between these events and study therapy.

40. Protocol/Study No. 011-065, AN 4930: A 66-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion. On Study Day 12 the patient experienced coronary artery occlusion, cardiogenic shock, and electromechanical dissociation. An arterial angiography was performed with angioplasty and stent placement, and a severe lesion on LDA was found. The procedure was successful; however, 35 minutes later the patient experienced cardiogenic shock, electromechanical dissociation and died. The investigator felt that there was no relationship between these events and study therapy.

41. Protocol/Study No. 011-064, AN 4956: A 57-year-old male with a history of CVA and CABG procedure was randomized to receive heparin. The patient completed the 48-hour study drug infusion. On Study Day 16 the patient underwent a CABG procedure. After the surgery the patient experienced decreased blood pressure and ventricular fibrillation. After defibrillation he experienced asystole. A re-thoracotomy was performed. The patient again experienced asystole and died. The investigator felt that there was no relationship between these events and study therapy.

42. Protocol/Study No. 011-061, AN 4972: A 67-year-old male was randomized to receive heparin. On Day 2 the patient experienced worsening unstable angina that was considered life-threatening. However, the patient did complete the 48-hour study drug infusion. The patient underwent a coronary angiography on Day 4 and upon returning to the ward, right arm dysfunction was noted. It is likely the patient had a CVA during the angiography procedure. The next day the patient suffered a non-Q-wave myocardial infarction. The patient continued to have chest pain, and because of this the patient underwent CABG surgery. The coroner's report recorded that the patient may have suffered a cerebral embolism prior to the surgery. While on anesthetic for the CABG it was noted that he developed swelling of the right side of the neck due to the placement of an external jugular catheter. The hematoma was released; however, at the end of the procedure it was apparent that he had suffered a cerebral infarction. The patient died on Day 7. The coroner's report concluded that the cause of death was due to a posterior cerebral infarction, most likely due to basilar artery thrombosis around the time of the coronary angiography. There was no evidence of intracerebral hemorrhage and there was no evidence of an early infarction in the anterior cerebral territory. The investigator felt that there was no relationship between these events and study therapy.

43. Protocol/Study No. 011-079, AN 5028: A 75-year-old male with a history of myocardial infarction was randomized to receive heparin. The patient completed the 48-hour study drug infusion. The patient experienced refractory angina and a new myocardial infarction on Study Day 5. On the same date an angiography was performed and the patient underwent a CABG procedure. He subsequently experienced worsening heart failure due to papillary muscle rupture. Finally, the patient died on Study Day 11. The cause of death was worsening heart failure. The investigator felt that there was no relationship between these events and study therapy.

44. Protocol/Study No. 011-160, AN 5123: A 49-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident and was subsequently discharged. On Study Day 28 the patient died. The probable cause of death was myocardial infarction. The investigator felt that there was no relationship between the patient's experience and study therapy.

45. Protocol/Study No. 011-160, AN 5130: A 58-year-old male with a history of nephrolithiasis and seminoma was randomized to receive heparin. The patient terminated the study drug infusion prematurely due to a protocol deviation and was subsequently discharged. On Study Day 26 the patient was found dead in bed in the morning by his wife. The patient's wife reported that her husband had no worsening of symptoms the previous evening. The patient was not examined postmortem. The cause of death was unknown. The investigator felt that there was no relationship between the patient's experience and study therapy.

**8.1.1.1e** Death Narratives from the **PRISM** trial (protocol **#011-) (cont)**

Heparin Group

46. **Protocol/Study** No. 011-061, AN 5160: A 79-year-old female with a history of myocardial infarction was randomized to receive heparin. The patient completed the 48-hour study drug infusion. On Day 7 the patient underwent an angiography and developed a hematoma in the right groin. The next day she was noted to be hypotensive with a blood pressure of 90/40. The patient's cardiac enzymes and ECG were normal. Later that morning her hematoma had increased in size with a drop in hemoglobin of approximately 20 g/L. The patient was transfused five units of packed red blood cells and was reviewed by the vascular surgeon. An ultrasound confirmed a pseudoaneurysm; this was repaired and the hematoma in the right groin evacuated. Although the patient's blood pressure had improved to 115/70 she remained unstable during the procedure with hypotension and clinically was peripherally shut down. The patient did not revive from the procedure. Subsequently, she developed abdominal distention and features of septic shock. On Day 9 she underwent a laparotomy that showed that her small and large bowel had infarcted with associated purulent peritonitis. She died later that day. The investigator felt that there was no relationship between these events and study therapy.

47. Protocol/Study No. 011-163, AN 5192: A 70-year-old male with a history of myocardial infarction was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident. On Study Day 8 the patient died. The cause of death was a possible cardiac rupture. The investigator felt that there was no relationship between the patient's experience and study therapy.

48. Protocol/Study No. 011-120, AN 5302: A 74-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident. On Study Day 6 the patient underwent bypass surgery due to persistent unstable angina and triple-vessel disease. The patient experienced an intestinal vascular insufficiency the next day. The patient underwent a total enterectomy procedure due to the embolism. The patient died on Study Day 15. The investigator felt that there was no relationship between these events and study therapy.

49. Protocol/Study No. 011-114, AN 5661: An 85-year-old female with a history of heart failure was randomized to receive heparin. The patient completed the 48-hour study drug infusion without incident. On Study Day 3 the patient developed adult respiratory distress syndrome and was intubated for artificial ventilation. The patient did not recover and died on Study Day 5. The investigator felt that there was no relationship between the patient's experience and study therapy.

50. Protocol/Study No. 011-125, AN 5687: A 69-year-old male was randomized to receive heparin. On Study Day 1 the patient experienced severe heart failure. The patient continued to receive the study drug infusion for the full 48-hour duration while being treated for heart failure. The patient also experienced an episode of bradycardia and subsequent episodes of tachycardia. Twelve days later the patient was in cardiogenic shock and died. The investigator felt that there was no relationship between the patient's experience and study therapy.

51. Protocol/Study No. 011-125, AN 5694: A 78-year-old male was randomized to receive heparin. The study drug therapy was prematurely discontinued on Study Day 2. The patient experienced pulmonary edema and subsequently died on Study Day 3. The investigator felt that there was no relationship between these events and study therapy.

52. Protocol/Study **No. 011-084,** AN 6383: A 74-year-old female was randomized to receive heparin. The study drug infusion was discontinued after the patient experienced pulmonary edema on Day 2 due to myocardial ischemia. Immediately afterwards the patient experienced apnea, was subsequently intubated and resuscitated, but died. The cause of death was felt to be myocardial infarction. The investigator felt that there was no relationship between these events and study therapy.

53. Protocol/Study No. 011-113, AN 6490: An 82-year-old male was randomized to receive heparin. After 45 hours of study drug therapy the patient met the endpoint of refractory angina. The investigator site discontinued the study drug therapy at this time. A coronary angiography revealed the following fmdings: (1) a 90% calcified stenosis of the left main coronary artery; (2) 90% stenosis of the right coronary artery; (3) 80% stenosis of circumflex artery; and (4) 80% stenosis of first diagonal artery. The patient underwent two PTCA procedures that failed. Medical therapy of heparin and trinitrin was unable to stabilize the refractory angina. The patient died on Study Day 6. The cause of death was considered left main coronary artery thrombosis. The investigator felt that there was no relationship between these events and study therapy.

54. Protocol/Study No. 011-157, AN 6531: A 79-year-old female was randomized to receive heparin. The patient completed the 48-hour study drug infusion. She subsequently experienced pulmonary edema on Day 4. On Day 8 the patient experienced cardiogenic shock and died the next day. The investigator felt that there was no relationship between the patient's experience and study therapy.

**8.1.1.1e** Death Narratives from the PRISM trial (protocol #011-) (cont)

Heparin Group

55. Protocol/Study No, 011-155, AN 6581: A 73-year-old male was randomized to receive heparin. The patient completed the 48-hour study drug infusion and subsequently underwent a CABG procedure. On Study Day 20 the patient experienced pneumonia despite ventilation and antibiotics. A diagnosis of renal insufficiency was made on Day 24. Five days later the patient developed hypotension and subsequently died. The cause of death was identified as pneumonia. The investigator felt, that there was no relationship between these events and study therapy.

56. Protocol/Study No. 011-070, AN 6736: A 61-year-old male with a history of myocardial infarction was randomized to receive heparin. The patient completed the 48-hour infusion uneventfully; however, he experienced three episodes of chest pain the next day. While receiving heparin and nitrate therapy the patient continued to experience chest pain. On Day 5 an ECG revealed anterolateral infarct with reciprocal changes. The patient then received recombinant tissue-type plasminogen activator. An urgent angioplasty was planned and upon arrival in the cardiac catheter lab the patient had a systolic cardiac arrest and subsequently died. The investigator felt that there was no relationship between these events and study therapy.

57. Protocol/Study No. 011-149, AN 6762: A 60-year-old male with a history of pulmonary edema, myocardial infarction, and bypass surgery was randomized to receive heparin. The patient completed the 48-hour infusion. The patient continued to experience chest pain and was referred for CABG. The patient's condition during the operation and during the immediate postoperation period was unremarkable. On Day 5, the patient's cardiac monitor showed a gradually broadening QRS complex. He became increasingly bradycardic and went into asystole. One hour later resuscitation was discontinued and the patient was declared dead. The primary cause of death was myocardial infarction due to ischemic heart disease. The investigator felt that there was no relationship between these events and study therapy.

58. Protocol/Study No. 011-072, AN 6810: An 83-year-old male with a history of myocardial infarction and PVD was randomized to receive heparin. The patient was discontinued from the study drug infusion on Day 1 due to the patient's continuing chest pain. Along with the patient's hemodynamic instability the investigator felt that the patient was having a myocardial infarction. The patient was given thrombolytic therapy. ECG postthrombolysis showed no improvement and the patient died later that night. The investigator felt that there was no relationship between these events and study therapy.

59. Protocol/Study No. 011-170, AN 6819: A 75-year-old male with a history of myocardial infarction and ventricular fibrillation was randomized to receive heparin. The patient was discontinued from the study on Day 2 due to the patient being referred for an urgent angioplasty. The patient's cardiac catheterization revealed double-vessel disease and left ventricular impairment. The patient then experienced heart failure and cardiogenic shock. An ECG also revealed ventricular tachycardia. A temporary pacing wire was inserted due to the patient's bradycardia and asystolic episode. The patient died on Day 4. The investigator felt that there was no relationship between these events and study therapy.

60. Protocol/Study No. 011-172, AN 6846: An 84-year-old female with a history of myocardial infarction and heart failure was randomized to receive heparin. The patient completed the 48-hour infusion; however, she continued to experience episodes of chest pain for the next several days. On Day 12 the patient continued to experience chest pain and was subsequently transferred to another facility for an emergency angiography and angioplasty. The treatment was unsuccessful and the patient died on the angiography table. The cause of death was coronary artery disease and cardiac arrest. The investigator felt that there was no relationship between these events and study therapy.

61. Protocol/Study No. 011-072, AN 7001: A 58-year-old male with a history of triple-vessel disease and myocardial infarction was randomized to receive heparin. The patient completed the 48-hour study drug infusion. On Day 7 the patient underwent a CABGprocedure. The patient was reported to be stable despite bleeding from chest drams. Lost fluid was replaced with four units of frozen fresh plasma, one unit of platelets, and six units of packed red blood cells. Two hours later the patient's blood pressure fell to 80/50. Oxygen levels deteriorated and pulmonary edema was confirmed by a chest X-ray. It was felt that the deterioration in the patient's condition was possibly due to an anaphylactic response to the blood products or acute sepsis. The patient's wound was reopened to investigate the cause of the bleeding. During the procedure the patient was very unstable and required adrenaline and noradrenaline to maintain blood pressure. Additional packed red blood cells, fresh frozen plasma, and pasteurized plasma protein were given as well. The patient's condition appeared to be more stable after the procedure; however, urinary output was poor, pupils were dilated, and the patient did not respond when suction was performed. Overnight the patient's condition deteriorated. The patient died on Day 8. The probable cause of death was anaphylactoid response to the fresh frozen plasma, which was reported to be severe. The investigator felt that there was no relationship between these events and study therapy.

**8.1.1.1e** Death **Narratives from the PRISM trial (protocol #011) (cont)**

Heparin Group

62. Protocol/Study No. 011124, AN 7245: A 77-year-old male was randomized. to receive heparin. The patient completed the 48-hour study drug infusion without incident. The patient was discharged on Study Day 18. The next day the patient died. The probable cause of death was sudden death. The investigator felt that there was no relationship between the patient's experience and study therapy.

**14.0.3** Deaths from RESTORE **(protocol #013)**

Through 30 days of follow-up, 96 subject deaths were reported for protocol #013 (A Randomized, Double-Blind, Placebo-Controlled Study of the Effects of Tirofiban (MK-0383) on Cardiac Outcomes in Patients Undergoing Percutaneous Transluminal Coronary Angioplasty or Atherectomy Due to Unstable Angina Pectoris or Following Acute Myocardial Infarction. *RESTORE).* At the end of 180 days of follow-up, *there were* 34 reported deaths.

Table 8.1.1.1f.l Deaths in the RESTORE trial"

| Time of Follow-up | Tirofiban +Heparin n=1071 | Heparin n=1070 | Total n=2141 |
|---|---|---|---|
| 48 hours | 2 (0.2%) | 2 (0.2%) | 4 (0.2%) |
| 7 days | 4 (0.4%) | 4 (0.4%) | 8 (0.8%) |
| 30 days | 9 (0.8%) | 8 (0.7%) | 17 (0.7%) |
| 180 days | 19 (1.8%) | 15 (1.4%) | 34 (1.6%) |

a. Data from NDA volume 1.55, reference 11, table 22.

The table below summarizes the causes of death for each of the 17 subjects in the RESTORE trial through 30 days, derived from the individual subject summaries. Four subject in the tirofiban arm (AN 1286, AN 1777, AN 2212, AN 3144), and two in the placebo group (AN 1425, AN 1445) had bleeding AEs, but the relationship only one (AN 1445, placebo group) seems clearly related to bleeding during study drug administration.

Table 8.1.1. 1f. 1 Deaths in the RESTORE trial'.

| Subject # | Day of Death | Cause(s) of Death |
|---|---|---|
| **Tirofiban[b]** | | |
| AN 1286 | 9 | Intercranial hemorrhage (on coumadin, ticlid, heparin, tirofiban and ASA) |
| AN 1513 | 22 | Sudden death/cardiac arrhythmia |
| AN 1777 | 11 | Retroperitoneal bleed<br>Pulmonary embolism |
| AN 1809 | 1 | MI, cardiogenic shock |
| AN 2212 | 8 | Coronary artery dissection, cardiogenic shock |
| AN 2708 | 2 | Ventricular fibrillation |
| AN 2765 | 5 | Ventricular tachycardia after groin hematoma requiring transfusion |
| AN 3144 | 2 | Post-op bleeding, LV aneurysm |
| AN 3250 | 3 | Sudden death at home |
| **Placebo[b]** | | |
| AN 1314 | 9 | FUO, sudden death at home |
| AN 1425 | 12 | Septicemia, hx of thrombocytopenia on methotrexate |
| AN 1445 | 2 | Retroperitoneal bleed<br>Thrombocytopenia |
| AN 1954 | 25 | CVA |
| AN 2903 | 3 | Ventricular fibrillation after emergent CABG |
| AN 2932 | 2 | Cardiogenic shock |
| AN 5109 | 13 | Ventricular fibrillation |
| AN 5243 | 4 | Heart failure |

a. Data from review of individual CRFs and from sponsor-generated death summaries

b. All subjects in the RESTORE trial also received ASA and heparin.

The subject narratives for the 17 deaths that occurred prior to the 30 day follow-up are below. No narrative information is available for the 17 deaths that occurred between 30 and 180 days. Following are details regarding the 17 patients who died within 30 days of completion of the study drug infusion.

14.0.3 Death Narratives from **RESTORE** (protocol **#013)**

Tirofiban (+Heparin) Group

1. AN **1286/Study** 013-003: A 67 year old male, suffered an intracranial hemorrhage on Day 2 PTCA. He was treated with tirofiban from Day 2 through Day 3. At the time of the intracranial hemorrhage, in addition to tirofiban he was receiving heparin, aspirin, coumadin and ticlopidine. He died on Day 9. The intracranial hemorrhage and death were considered by the investigator to be possibly related to the study drug. (Note: This patient had been studied just prior to the Steering Committee's recommendation to discontinue study drug in the event of stent implantation, and in fact was a contributing factor to that recommendation. However, even prior to that recommendation, the use of multiple anticoagulants in this manner represented a protocol violation.)

2. AN **1513/Study** 013-076: A 76 year old male received tirofiban in conjunction with angioplasty. He experienced some mild bleeding following the procedure but study drug infusion was completed. He was discharged. On Day 22 he collapsed suddenly while walking at home and died. There had been no complaint of chest pain prior to the collapse. He was pronounced dead by an EMS team at the site. The cause of death was cardiac arrhythmia. The arrhythmia and death were considered by the investigator to be definitely not related to the study drug.

3. AN **1777/Study** 013-064: A 72 year old male received tirofiban in conjunction with angioplasty. Early the next morning he complained of abdominal pain and was unable to void. Heparin and study drug were discontinued. A Foley was placed, and the patient received 2 units of packed RBCs over the next day, and his condition stabilized. A CT scan confirmed bleeding of retroperitoneal origin. He received 2 additional units of packed RBCs and was discharged. At home, the patient suffered a pulmonary embolism and died on day Day 11 at a different hospital. The events were considered by the investigator to be probably not related to the study drug.

4. AN **1809/Study** 013-021: A 73 year old male received tirofiban in conjunction with an atherectomy following an acute M.I. During the procedure, he required placement of a stent and an intra-aortic balloon pump. Study drug was discontinued. Following the procedure, he developed hypotension associated with a retroperitoneal hemorrhage and cardiac tamponade. He was taken to the operating room for emergency CABG, but died in the OR. Cause of death was attributed to cardiogenic shock. The events leading to the patient's death were considered by the investigator to be probably not related to the study drug.

5. AN **2212/Study** 013-101: A 68 year old male received tirofiban in conjunction with angioplasty following an acute M.I. During the procedure the patient developed a dissection of the mid-LAD with distal embolization. Two stents were placed in addition to an intra-aortic balloon pump. Study drug was discontinued. His condition worsened with progression of preexisting heart failure, as well as confusion, ventricular tachycardia, and cardiogenic shock. He died on Day 8 as a result of cardiogenic shock. The events leading to the patient's death were not considered by the investigator to be related to the study drug.

6. AN **2708/Study** 013-021: A 77 year old female received tirofiban in conjunction with angioplasty following an acute M.I. She experienced ventricular fibrillation prior to receiving study drug. The PTCA was completed but the patient experienced ventricular fibrillation after the procedure from which she was resuscitated. Study drug was interrupted. On return to her room she was hypotensive and unresponsive and had a slow agonal rhythm. Study drug was restarted but was discontinued when a few drops of blood were noted on the endotracheal tube, most likely related to traumatic intubation. There was no gross bleeding. She developed ventricular fibrillation and expired on Day 1. Cause of death was attributed to ventricular fibrillation and progression of the prestudy acute M.I. The events leading to the patient's death were considered by the investigator to be probably not related to the study drug.

7. AN **2765/Study** 013-014: A 67 year old female had an angioplasty, and received tirofiban for three days. She experienced oozing from the catheterization site and a small groin hematoma. Her hemoglobin and hematocrit were low and she received packed RBCs and was discharged on Day 5. That evening she was admitted to the emergency room with supraventricular tachycardia and died (Day 5). No autopsy was performed, but the cause of death was suspected to be septic shock. The groin bleeding was considered to be related to the study drug, but the other events were not considered by the investigator to be related.

8. AN **3144/Study** 013-003: A 75 year old male suffered an acute M.I. and underwent angioplasty. Tirofiban was given during and following the procedure. On Day 2, the patient was still experiencing chest pain and a TEE showed a large left ventricular aneurysm. He underwent surgery for CABG and repair of the LV aneurysm. He developed a GI bleed, respiratory failure requiring intubation, renal insufficiency, pulmonary edema, a pleural effusion, and right subclavian vein thrombosis. A repeat TEE showed a recurring LV aneurysm, and the patient underwent a difficult surgical procedure, requiring transfusion of several units of plasma intraoperatively. Though the patient survived the procedure, he died later that evening (Day 29) of cardiac arrest. All the events were considered by the investigator to be probably not related to the study drug.

14.0.3 Death Narratives from RESTORE (protocol #013) (cont)

Tirofiban (+Heparin) Group

9. AN 3250/Study 013-014: A 73 year old female underwent angioplasty and received tirofiban during the procedure. Her platelet count dropped to 93,000/mm$^3$, down from a baseline of 163,000/mm$^3$, and the study drug was discontinued. The platelet count returned to 115,000/mm$^3$ over the next day, and the patient was released on Day 3 with no complaints. That evening (Day 3), she died at home. Cause of death is unknown, and no autopsy was performed. The death was considered by the investigator to be probably not related to the study drug.

Placebo (+Heparin) Group

1. AN 1314/Study 013-045: A 53 year old male received placebo in conjunction with angioplasty. The procedure was completed without complication and study drug infusion was completed. The patient was discharged. On Day 9, he was admitted with fever of unknown origin, but a work-up was negative and he was discharged. On Day 22 he was found unresponsive in his yard with his car keys and his medication. He was transported to the ER via EMS and despite resuscitation attempts he died. No autopsy report was available, but the cause of death was a suspected M.I. The patient's death was considered by the investigator to be probably not related to the study drug.

2. AN 1425/Study 013-014: A 68 year old female had an angioplasty, and received placebo during the procedure. She returned to the catheterization lab later in the day with recurrent chest pain, and study drug was discontinued. She was subsequently diagnosed with septicemia for which she received several antibiotics. On Day 12 her platelet count was 95,000/mm, down from a baseline of 289,000/mm$^3$; the platelet drop was considered to be due to septicemia and metbotrexate she was taking for arthritis. Her condition deteriorated, she developed a GI bleed, and heart failure, and on Day 18 she died due to septicemia. The patient's death and associated adverse experiences were not considered by the investigator to be related to the study drug.

3. AN 1445/Study 013-030: A 71 year old female received placebo in conjunction with angioplasty. The procedure was completed without significant complications. Later in the day, the patient complained of right flank pain, and experienced a drop in blood pressure. A CT scan revealed a large retroperitoneal bleed. She received multiple transfusions of packed RBCs, fresh frozen plasma, platelets, and I.V. fluids, and required pressor support. Her platelet count dropped to 82,000/mm$^3$ from a baseline of 238,000/mm$^3$. Study drug and heparin were discontinued. The patient died the next morning (Day 2) despite extensive volume replacement. Cause of death was attributed to retroperitoneal hemorrhage. The investigator unblinded the study drug. The events leading to the patient's death were considered by the investigator to be definitely not related to the study drug.

4. AN 1954/Study 013-053 A 72 year old male received placebo in conjunction with angioplasty. Stent implantation was required during the procedure due to a dissection. Study drug was discontinued and the patient was placed on ticlopidine, and was discharged on Day 4. On Day 25, the patient suffered a CVA and expired on Day 26. The CVA was not considered by the investigator to be related to the study drug.

5. AN 2903/Study 013-052: A 64 year old female received placebo in conjunction with angioplasty. The procedure was completed but with some compromised flow to side branches. She also experienced considerable catheterization site bleeding (considered to be possibly drug related by the investigator) at the time of sheath removal, which required administration of fluids. Bleeding was controlled by application of a Femstop device. She experienced chest pain later. in the day, as well as ventricular tachycardia. A catheterizatio revealed total occlusion of the angioplasty site. She developed a sudden drop in blood pressure and heart rate on Day 2, with agonal breathing. CPR was initiated, percutaneous cardiopulmonary bypass was achieved, and she was transferred to the OR were she underwent a four-vessel CABG. On Day 3, she developed ventricular tachycardia that progressed to ventricular fibrillation. Resuscitation was unsuccessful and the patient died. The events leading to the patient's death were not considered by the investigator to be related to the study drug.

6. AN 2932/Study 013-020: A 58 year old male received placebo in conjunction with angioplasty. The next day, he developed complete heart block and heart failure. Study drug was discontinued due to groin hematoma and femoral bruit. He was intubated for respiratory failure and remained hypotensive. He died later in the day (Day 2) due to cardiogenic shock. The events leading to the patient's death were considered by the investigator to be probably not related to the study drug.

7. AN 5109/Study 013-109: A 67 year old female received placebo in conjunction with angioplasty. During the procedure she required stent placement, and study drug was discontinued. On Day 9, while still hospitalized, the patient developed ventricular fibrillation and died on Day 13 as a result. The v-fib and death were considered by the investigator to be definitely not related to the study drug.

8. AN 5243/Study 013-107: A 79 year old male received placebo in conjunction with angioplasty. Over the next day, the patient deteriorated and developed heart failure and bradycardia. The study drug infusion was completed. Despite pharmacological support, he died on Day 4. Cause of death was attributed to heart failure. The events were considered by the investigator to be probably not related to the study drug.

## 15.0 Appendix Three: Listing Of Subjects With Serious Adverse Events (SAEs)

The following sources were used for this appendix:

1. NDA volume 1.42, table 46 (PRISM-PLUS);
2. NDA volume 1.48, table 45 (PRISM);
3. NDA volume 1.55 table 41 (RESTORE).

Listed SAEs are provided by the sponsor, and have not been independently confirmed through CRFs evaluation by the FDA.

### 15.0.1 Subjects in Tirofiban group with serious adverse events (SAEs)

Table 15.0.1.1 SAEs in the tirofiban group from the phase III trials.

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| | | | | | |
| **TIROFIBAN** | | | | | |
| ***PRISM-PLUS TRIAL*** | | | | | |
| 006-004 AN 5135 | 64, F | 9 | Heart failure | None | Recovered |
| | | | Respiratory Distress Syndrome | None | Recovered |
| 006-008 AN 5013 | 66, F | 1 | Drug Overdose | Interupted | Recovered |
| 006-008 AN 5016 | 87, M | 8 | Hematoma | None | Recovered |
| 006-008 AN 5098 | 71, M | 7 | Death | Death | Death |
| | | 6 | Septicemia | Death | Death |
| | | 5 | Vascular Insufficiency, Intestinal | Death | Death |
| 006-008 AN 5100 | 70, M | 28 | Pulmonary Edema | None | Recovered |
| 006-008 AN 5146 | 76, M | 3 | Death<br>Cardiogenic Shock<br>Pulmonary Edema | Death | Death |
| 006-013 AN 5059 | 75, M | 28<br>24 | Intestinal Obstruction<br>Cerebrovascular Accident | None<br>None | Recovered |
| 006-029 AN 6477 | 47. M | 4<br>4 | Cardiac arrest<br>Ventricular fibrillation | None<br>None | Recovered<br>Recovered |
| 006-032 AN 6368 | 70, F | 3 | Gastric hemorrhage | D/C'd | Recovered |
| 006-032 AN 6623 | 77, F | 5<br>5<br>4<br>2<br>2 | Death<br>Ventricular fibrillation<br>Cerebrovascular accident<br>AV block, 3rd degree<br>Asystole | Death<br>None<br>D/C'd<br>Interrupted<br>Interrupted | Death |
| 006-033 AN 6131 | 69, M | 5<br>5 | Death<br>Cardiogenic shock | Death<br>None | Death |
| 006-033 AN 6166 | 81, F | 7<br>7<br>7 | Death<br>Cardiac arrest<br>Coronary atherosclerosis | Death<br>None<br>None | Death |
| 006-034 AN 6085 | 71, M | 4 | GI hemorrhage | None | Recovered |
| 006-034 AN 6520 | 67, F | 13<br>13 | Heart failure<br>Unstable angina | None<br>None | Recovered<br>Recovered |
| 006-034 AN 6524 | 83, F | 3<br>2 | Death<br>Cardiogenic shock | Death<br>None | Recovered |
| 006-034 AN 6595 | 70, F | 9<br>9 | Death<br>Cardiac arrest | Death<br>None | Death |
| 006-034 AN 6600 | 68, M | 14 | Unstable angina | None | Recovered |
| 006-034 AN 6601 | 52, M | 5 | Ventricular fibrillation | None | Recovered |
| 006-035 AN 6377 | 45, M | 18 | Unstable angina | None | Recovered |
| 006-036 AN 6236 | 59, M | 6<br>6 | Death<br>Pulmonary embolism | Death<br>None | Death |
| 006-037 AN 6002 | 77, M | 14<br>9 | CVA<br>Cardiogenic shock | None<br>None | Recovered<br>Recovered |
| 006-037 AN 6074 | 67, F | 1 | Drug Overdose | None | Recovered |
| 006-037 AN 6077 | 63, F | 15 | Phlebitis/thrombophebitis | None | Recovered |

15.0.1 Subjects in **Tirofiban** group with serious adverse events **(SAEs) (cont)**

Table 15.0.1.1 SAEs in the tirofiban group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| TIROFIBAN | | | | | |
| *PRISM-PLUS TRIAL* | | | | | |
| 006-037 AN 6340 | 68, M | 10<br>10<br>10 | Death<br>Cardiogenic shock<br>Cardiac arrest | Death<br>None<br>None | Death |
| 006-037 AN 6560 | 64, F | 21 | Arm pain | None | Recovered |
| 006-038 AN 6543 | 73, M | 5 | Hematoma | None | Recovered |
| 006-038 AN 6670 | 80, F | 3<br>9 | Bleeding, postoperative<br>Bleeding, postoperative | None | Recovered |
| 006-040 AN 6204 | 55, M | 30 | Unstable angina | None | Recovered |
| 006-041 AN 6029 | 73, M | 3 | Transient ischemic attack | None | Recovered |
| 006-042 AN 6044 | 61, M | 23 | Pneumonia | None | Recovered |
| 006-042 AN 6350 | 55, M | 9 | Unstable angina | None | Recovered |
| 006-042 AN 6862 | 51, M | 8<br>8 | Ventricular fibrillation<br>Ventricular tachycardia | None | Recovered |
| 006-044 AN 6141 | 60, M | 14<br>14<br>1 | Cardiac tamponade<br>Bleeding, postoperative<br>Drug overdose | None<br>None<br>None | Recovered |
| 006-044 AN 6250 | 73, M | 4<br>5<br>5<br>4 | Abdominal pain<br>Death<br>Electromechanical dissociation<br>GI (Anal/rectal) hemorrhage | Death<br><br><br>D/c'd | Death |
| 006-044 AN 6277 | 79, M | 8 | Cardiomyopathy | None | Recovered |
| 006-044 AN 6280 | 64, M | 23 | Phlebitis/thrombophebitis | None | Recovered |
| 006-044 AN 6281 | 75, M | 6<br>27<br>1 | Pulmonary edema<br>Myocardial infarction<br>Drug overdose | None | Recovered |
| 006-044 AN 6823 | 61, M | 26<br>26 | Suicide attempt<br>Depressive disorder | None | Recovered |
| 006-044 AN 6833 | 80, F | 23 | Hemoptysis | None | Recovered |
| 006-044 AN 6838 | 72, M | 3 | Pulmonary edema | None | Recovered |
| 006-044 AN 7072 | 49, M | 28<br>27<br>4 | Death<br>Ventricular fibrillation<br>Ventricular tachycardia | Death<br>None<br>None | Death |
| 006-044 AN 7080 | 55, F | 16<br>5<br>4 | Phlebitis/thrombophebitis<br>Pseudoaneurysm<br>Hemorrhage | None | Recovered |
| 006-044 AN 7100 | 57, F | 7 | Hemorrhage | None | Recovered |
| 006-045 AN 6057 | 61, M | 6<br>5 | Death<br>Cardiogenic shock | Death<br>None | Death |
| 006-045 AN 6059 | 74, F | 31 | Urolithiasis | None | Recovered |
| 006-045 AN 6290 | 66, F | 4<br>4 | Death<br>Myocardial rupture | Death<br>None | Death |
| 006-045 AN 6302 | 63, F | 28 | Unstable angina | None | Recovered |
| 006-045 AN 6661 | 54, F | 26 | Chest pain | None | Recovered |
| 306-046 AN 6160 | 68, F | 2 | Drug overdose | Interuppted | Recovered |
| 006-047 AN 5177 | 69, F | 5<br>5 | Death<br>Sudden cardiac death | Death<br>None | Death |
| 006-048 AN 7240 | 75, M | 17<br>3<br>3 | Death<br>Pulmonary edema<br>Septicemia | Death<br>None<br>None | Death |
| 006-048 AN 7245 | 75, M | 6 | Septicemia | None | Recovered |
| 006-048 AN 7246 | 69, M | 23 | Hypovolemia | None | Recovered |

15.0.1 Subjects in **Tirofiban** group with serious adverse events **(SAEs) (cont)**

Table 15.0.1.1 SAEs in the tirofiban group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| | | | | | |
| TIROFIBAN | | | | | |
| ***PRISM-PLUS TRIAL*** | | | | | |
| 006-049 AN 6318 | 83, F | 11<br>16<br>11<br>11 | Shock<br>Pulmonary edema<br>Retroperitoneal hemorrhage<br>Hematome | None | Recovered |
| 006-049 AN 6589 | 48, M | 27 | Wound dehiscence | None | Recovered |
| 006-050 AN 6544 | 47,M | 30 | Chest pain | None | Recovered |
| 006-050 AN 6547 | 61, F | 8<br>8<br>8 | Death<br>Cardiogenic shock<br>Heart surgery, complication | Death<br>None<br>None | Death |
| 006-050 AN 6695 | 82, F | 7<br>6<br>7 | Death<br>Pulmonary edema<br>Cardiogenic shock | Death<br>None<br>None | Death |
| 006-050 AN 6701 | 71, F | 6 | Hematoma | None | Recovered |
| 006-053 AN 5165 | 66, M | 3<br>3<br>3 | Death<br>Pulmonary edema<br>Cardiogenic shock | Death<br>None<br>None | Death |
| 006-055 AN 6177 | 72, F | 4<br>5 | Bleeding, postoperative<br>Bleeding, postoperative | None | Recovered |
| 006-057 AN 6615 | 81, M | 4<br>4<br>4 | Death<br>Cardiogenic shock<br>Electromechanical dissociation | Death<br>None | Death |
| 006-058 AN 6424 | 61,M | 18 | Unstable angina | None | Recovered |
| 006-058 AN 6427 | 65, F | 1 | Drug overdose | None | Recovered |
| 006-060 AN 6033 | 73, M | 5 | Bradycardia | None | Recovered |
| 006-062 AN 6643 | 52, M | 14 | Pneumothorax | None | Recovered |
| 006-064 AN 6357 | 74, M | 5<br>5 | Hematoma<br>Thrombocytopenia | None | Recovered |
| 006-064 AN 6582 | 67, F | 21<br>26 | Cardiac arrest<br>CVA | None<br>None | Recovered |
| 006-064 AN 6584 | 74, M | 2 | Pulmonary embolism | D/c'd | Recovered |
| 006-065 AN 6900 | 50, F | 7 | Cardiogenic shock | None | Recovered |
| 006-067 AN 5264 | 65, F | 6<br>6<br>6 | Cardiac arrest<br>Death<br>Cardiogenic shock | Death<br>None | Death |
| 006-067 AN 5311 | 46, M | 20 | Pericardial effusion | None | Recovered |
| 006-080 AN 5203 | 75, F | 1 | Drug overdose | None | Recovered |
| 006-086 AN 7496 | 82, F | 16 | Unstable angina | None | Recovered |
| 006-086 AN 7530 | 80, M | 5 | Death | Death | Death |
| 006-094 AN 7617 | 37, M | 7<br>7<br>7<br>7 | GI hemorrhage<br>Shock<br>Respiratory Distress Syndrome<br>Gastritis | None | Recovered |
| | | | | | |

15.0.1 Subjects in **Tirofiban group with serious adverse events (SAEs) (cont)**

Table 15.0.1.1 SAEs in the tirofiban group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| **TIROFIBAN** | | | | | |
| ***PRISM-PLUS TRIAL*** | | | | | |
| 011-001 1014 | 71 F | 2 | Fever | None | Recovered |
| 011-002 1044 | 49 F | 4 | Bleeding, postoperative | None | Recovered |
| 011-002 1048 | 81 M | 2<br>2 | Hypotension<br>Bleeding, postoperative | None | Recovered |
| 011-004 1117 | 71 M | 2<br>2 | Diverticulum, intestinal<br>Hemorrhage, gastrointestinal | D/C'd | Recovered |
| 011-004 1118 | 50 M | 2<br>1 | Epistaxis<br>Drug overdose | None | Recovered |
| 011-004 1120 | 48 M | 26<br>26 | Infection, wound, postoperative<br>Infection, bone/cartilage | None | Recovered |
| 011-004 2199 | 71 M | 16 | Angina, unstable | None | Recovered |
| 011-004 2202 | 78 M | 13 | Effusion, pleural | None | Recovered |
| 011-004 2209 | 53 M | 24 | Angina, unstable | None | Recovered |
| 011-004 2453 | 57 M | 22 | Angina, unstable | None | Recovered |
| 011-005 1919 | 51 M | 9 | Ventricular fibrillation | None | Recovered |
| 011-005 1922 | 69 M | 1 | Drug overdose | None | Recovered |
| 011-006 1635 | 81 F | 29 | CVA | None | Continuing |
| 011-007 1458 | 52 M | 1 | Thrombocytopenia | None | Recovered |
| 011-008 1157 | 83 F | 8<br>9<br>6<br>6 | Thrombocytopenia<br>Tachycardia-bradycardia syndrome<br>Shock, cardiogenic<br>Occlusion, coronary artery | None | Recovered |
| 011-008 1160 | 72 F | 24 | Heart disorder, ischemic | None | Recovered |
| 011-008 2187 | 86 F | 4<br>3<br>4<br>3 | Death<br>Cardiac arrest<br>Cardiac arrest<br>Hypotension | None | Death |
| 011-008 2288 | 79 F | 4 | Hemorrhage, gastrointestinal | None | Recovered |
| 011-011 1451 | 77 M | 27 | Pneumonia, aspiration | None | Recovered |
| 011-011 1799 | 65 M | 3<br>18 | Respiratory failure<br>Enterocolitis, pseudomembranous | None | Recovered |
| 011-013 1280 | 65M | 28 | Angina, unstable | None | Recovered |
| 011-013 1699 | 67 M | 27 | Angina, unstable | None | Recovered |
| 011-013 2140 | 64 M | 14 | Infection, wound | None | Recovered |
| 011-016 1145 | 42 M | 6 | Drug overdose | None | Recovered |
| 011-016 1223 | 49 F | 14 | Angina, unstable | None | Recovered |
| 011-016 1241 | 46 M | 13 | Angina, unstable | None | Recovered |
| 011-016 1249 | 44 M | 1 | Drug overdose | None | Recovered |
| 011-016 1861 | 68 M | 17 | Hemorrhage, gastrointestinal, lower | None | Recovered |
| 011-020 1173 | 53 M | 2 | Drug overdose | None | Recovered |
| 011-021 1071 | 73 F | 8<br>4<br>8 | Death<br>Pneumonia<br>Respiratory failure | None | Death |
| 011-021 1239 | 73 M | 3<br>3 | Hemorrhage, gastrointestinal<br>Neoplasm, gastric | None | Recovered<br>Still present |
| 011-021 1724 | 72 M | 15<br>6 | Death<br>CVA | None | Death |
| 011-021 1725 | 55 F | 10 | Angina, unstable | None | Recovered |
| 011-021 1728 | 76 M | 24 | Angina, unstable | None | Recovered |
| 011-021 2128 | 66 F | 1 | Drug overdose | None | Recovered |
| 011-021 2131 | 65 M | 3 | Hemorrhage, intracranial | D/C'd | Recovered |

15.0.1 Subjects in Tirofihan group with serious adverse events **(SAEs) (cont)**

Table 15.0.1.1 SAEs in the tirofiban group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| TIROFIBAN | | | | | |
| *PRISM TRIAL* | | | | | |
| 011-021 2406 | 64 M | 15<br>8 | Ulcer, peptic<br>Pain, chest | None | Recovered |
| 011-021 2495 | 74 M | 23 | Angina, unstable | None | Continuing |
| 011-021 2553 | 53 M | 5<br>6 | Angina, unstable<br>Occlusion, coronary artery | None | Recovered |
| 011-023 2230 | 63 F | 10 | Angina, unstable | None | Recovered |
| 011-023 2325 | 61 F | 8 | Hemorrhage, retroperitoneal | None | Recovered |
| 011-023 2518 | 63 F | 8<br>8<br>8 | Death<br>Bleeding disorder<br>Multiple organ failure | None | Recovered |
| 011-024 1768 | 71 M | 19 | Atrial flutter | None | Recovered |
| 011-024 1773 | 81 F | 10<br>7<br>3 | Occlusion, arterial, lower extremity<br>Myocardial infarction<br>Dissection, coronary artery | None | Recovered |
| 011-024 1775 | 75 M | 8<br>13<br>7<br>15<br>7 | Atrial fibrillation<br>Bacteremia<br>Coagulation disorder<br>Dehiscence, wound<br>CVA | None | Recovered<br>Continuing<br>Recovered<br>Continuing<br>Continuing |
| 011-026 1416 | 54 F | 9 | Infection, urinary tract | None | Recovered |
| 011-032 1222 | 51 M | 4 | Bipolar disorder | None | Continuing |
| 011-032 1349 | 89 F | 8<br>8 | Death<br>Edema, pulmonary | None | Death |
| 011-032 1355 | 69 F | 24 | Embolism/infarction, pulmonary | None | Recovered |
| 011-032 1779 | 68 M | 13<br>2 | Angina, unstable<br>Drug overdose | None | Recovered |
| 011-032 1782 | 60 M | 7 | Postcardiotomy syndrome | None | Recovered |
| 011-032 1786 | 79 M | 15 | Pain, abdominal | None | Recovered |
| 011-032 2436 | 85 F | 6<br>6 | Gastritis<br>Diverticulum, intestinal | None | Recovered |
| 011-033 1028 | 49 M | 3 | CVA | None | Continuing |
| 011-033 2237 | 60 M | 6<br>8 | Hypoxemia<br>Hypoxemia | None | Recovered |
| 011-036 1053 | 63 M | 25 | Neoplasm, brain, malignant | None | Continuing |
| 011-042 1647 | 78 M | 9<br>17 | Ventricular tachycardia<br>Pneumothorax | None | Recovered |
| 011-042 1650 | 49 M | 4<br>4 | Ventricular fibrillation<br>Ventricular tachycardia | None | Recovered |
| 011-044 2806 | 38 M | 11<br>11<br>11 | Hypotension<br>Angina, unstable<br>Myocardial infarction | None | Recovered |
| 011-048 1266 | 47 M | 1 | Drug overdose | None | Recovered |
| 011-058 1654 | 51 M | 17 | Myocardial infarction, non-Q-wave | None | Recovered |
| 011-058 1661 | 63 M | 31<br>30<br>30 | Death<br>Pneumonia<br>COPD | None | Death |
| 011-058 2173 | 76 F | 25 | Angina, unstable | None | Recovered |
| 011-058 2421 | 55 M | 13<br>22<br>1 | Cardiac arrest<br>Edema, pulmonary<br>Drug overdose | None | Recovered |
| 011-058 2424 | 73 M | 8 | Ventricular tachycardia | None | Recovered |

15.0.1 Subjects in **Tirofiban** group with serious adverse events **(SAEs) (cont)**

Table 15.0.1.1 SAEs in the tirofiban group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| TIROFIBAN | | | | | |
| *PRISM TRIAL* | | | | | |
| 011-059 4010 | 60 M | 3 | Heart failure | None | Recovered |
| 011-059 4616 | 54 M | 15 | Angina, unstable | None | Recovered |
| 011-060 4040 | 37 F | 9 | GI hemorrhage, anal/rectal | None | Recovered |
| 011-061 3094 | 71 M | 1 | Melena | None | Recovered |
| 011-061 3098 | 71 F | 12<br>12<br>10 | Death<br>Sudden cardiac death<br>Syncope | None | Death |
| 011-061 3252 | 56 M | 1 | Drug overdose | None | Recovered |
| 011-061 3256 | 72 M | 17 | Embolism/infarction, pulmonary | None | Recovered |
| 011-061 3261 | 55 F | 1 | Drug overdose | None | Recovered |
| 011-061 3620 | 73 M | 18<br>8<br>11<br>11<br>11<br>13<br>11 | Death<br>Hypotension<br>Coma Severe<br>Brain damage, anoxic<br>CVA<br>Septicemia<br>CVA | None | Death |
| 011-061 3623 | 81 M | 1 | Drug overdose | None | Recovered |
| 011-061 3627 | 63 M | 14 | Urinary retention | None | Recovered |
| 011-061 3632 | 67 F | 23 | Pain, musculoskeletal | None | Recovered |
| 011-061 4792 | 51 M | 8 | Angina, unstable | None | Recovered |
| 011-061 7550 | 78 F | 4<br>1<br>4<br>1 | Death<br>Cardiac arrest<br>Cardiac arrest<br>Shock, cardiogenic | None | Death |
| 011-061 7553 | 80 F | 23 | CVA | None | Recovered |
| 011-061 7557 | 63 M | 8 | Angina, unstable | None | Recovered |
| 011-062 3076 | 70 M | 4<br>4 | Death<br>Ventricular fibrillation | None | Death |
| 011-063 3929 | 69 M | 7 | Death | None | Death |
| 011-063 3936 | 70 M | 13 | Angina, unstable | None | Recovered |
| 011-064 3605 | 47 F | 1 | Thrombocytopenia | None | Recovered |
| 011-064 3611 | 61 M | 1 | Drug overdose | None | Recovered |
| 011-064 4958 | 62 M | 12 | Angina, unstable | None | Recovered |
| 011-065 3286 | 52 M | 19<br>9<br>9<br>14 | Death<br>Rhabdomyolysis<br>Renal insufficiency<br>Shock, cardiogenic | None | Death |
| 011-065 3527 | 45 F | 16 | Death | None | Death |
| 011-065 4940 | 75 M | 2<br>2<br>2 | Death<br>Cardiac arrest<br>Electromechanical dissociation | D/C'd | Death |
| 011-066 2913 | 59 M | 8 | Embolism/infarction, pulmonary | None | Recovered |
| 011-066 3103 | 76 F | 20 | Angina, unstable | None | Recovered |
| 011-066 3287 | 67 M | 22 | Angina, unstable | None | Recovered |
| 011-066 3291 | 65 M | 6 | Pulmonary function abnormality | None | Recovered |
| 011-066 3544 | 51 M | 12 | Infection, postoperative | None | Recovered |

**15.0.1** Subjects in Tirofiban group with serious adverse events **(SAEs) (cont)**

Table 15.0.1.1 SAEs in th tirofiban group om the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| TIROFIBAN | | | | | |
| *PRISM TRIAL* | | | | | |
| 011-066 3737 | 65 F | 13 | CVA | None | Recovered |
| 011-069 6655 | 79 F | 1 | Drug overdose | D/C'd | Recovered |
| 011-069 6686 | 74 M | 3 | Fistula, arteriovenous | None | Recovered |
| 011-069 7173 | 55 F | 23 | Dyspnea | None | Recovered |
| 011-070 4325 | 59 M | 11 | Pain, chest | None | Recovered |
| 011-070 4326 | 50 M | 7 | Angina pectoris | None | Recovered |
| 011-070 4369 | 42 M | 20 | Angina pectoris | None | Recovered |
| 011-070 4372 | 70 M | 18<br>18 | Hypotension<br>Bleeding, postoperative | None | Recovered |
| 011-070 4398 66 | 66 M | 32<br>12<br>17<br>28<br>17<br>14<br>17<br>14<br>22 | Death<br>Edema, pulmonary<br>Acidosis<br>Renal insufficiency<br>Septicemia<br>Fever<br>Mediastinitis<br>Infection, wound<br>Respiratory distress syndrome | None | Death |
| 011-070 6565 | 66 M | 9<br>4 | Pain, musculoskeletal<br>Occlusion, coronary artery | None | Recovered |
| 011-070 6725 | 60 F | 22 | Embolism/infarction, pulmonary | None | Recovered |
| 011-070 6730 | 46 M | 16<br>16 | Gastritis<br>Duodenitis | None | Continuing |
| 011-070 6735 | 65 M | 11 | Pain, chest | None | Recovered |
| 011-071 6569 | 73 M | 1 | Drug overdose | None | Recovered |
| 011-072 4362 | 61 M | 4 | Pain, chest | None | Recovered |
| 011-072 4365 | 65 M | 7 | Angina, unstable | None | Recovered |
| 011-072 6607 | 78 M | 6<br>6 | Hypotension<br>Hypotension | None | Recovered |
| 011-072 6610 | 85 M | 6 | Edema, pulmonary | None | Recovered |
| 011-072 6812 | 74 F | 9<br>20 | Constipation<br>Infection, bacterial | None | Recovered |
| 011-072 6861 | 77 M | 1 | Drug overdose | None | Recovered |
| 011-072 6862 | 53 M | 1 | Drug overdose | None | Recovered |
| 011-072 7005 | 72 M | 13<br>12 | Death<br>Vascular insufficiency, intestinal | None | Death |
| 011-074 1038 | 52 F | 5 | Ventricular tachycardia | None | Recovered |
| 011-074 2319 | 43 F | 5<br>4 | Renal insufficiency<br>Hematoma | None | Recovered |
| 011-076 3578 | 65 F | 25 | Heart failure | None | Recovered |
| 011-076 3697 | 69 F | 30<br>30 | Death<br>Sudden death | None | Death |
| 011-077 3057 | 49 M | 14 | Angina, unstable | None | Recovered |
| 011-077 3058 | 51 M | 22<br>29 | Myocardial infarction, non-Q-wave<br>Myocardial infarction, non-Q-wave | None | Recovered |
| 011-077 3702 | 55 F | 1 | Drug overdose | None | Recovered |

15.0.1 Subjects in Tirofiban **group with** serious adverse events **(SAEs) (cont)**

Table 15.0.1.1 SAEs in the tirofiban group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| **TIROFIBAN** | | | | | |
| *PRISM TRIAL* | | | | | |
| 011-077 3703 | 46 F | 8 | Angina, unstable | None | Recovered |
| 011-077 5432 | 33 M | 14<br>1 | Pain, chest<br>Drug overdose | None | Recovered |
| 011-077 7413 | 73 M | 8<br>33<br>19<br>21<br>25 | Infection, wound<br>Infection, bacterial<br>GI hemorrhage, Ulcer, duodenal w/hemorrhage<br>Ulcer, duodenal w/hemorrhage<br>Ulcer, duodenal w/hemorrhage | None | Recovered |
| 011-078 3065 | 57 M | 4 | Edema, pulmonary | None | Recovered |
| 011-078 3067 | 74 F | 23 | Myocardial infarction, non-Q-wave | None | Recovered |
| 011-078 3590 | 54 M | 24 | Angina, unstable | None | Recovered |
| 011-079 3271 | 55 M | 17 | Pseudoaneurysm | None | Recovered |
| 011-079 3497 | 64 F | 24 | Angina, unstable | None | Recovered |
| 011-079 3502 | 68 M | 18<br>16<br>16 | Death<br>Hypotension<br>Heart failure | None | Death |
| 011-I 17 3793 | 58 F | 29 | Angina, unstable | None | Recovered |
| 011-I 19 4387 | 60 M | 23 | Atrial fibrillation | None | Recovered |
| 011-119 4388 | 58 M | 9 | Myocardial infarction, non-Q-wave | None | Recovered |
| 011-119 6602 | 52 M | <br>25 | Infection, respiratory<br>Infection, wound | None | Recovered |
| 011-120 5296 | 75 M | 1 | Edema, pulmonary | None | Recovered |
| 011-120 5297 | 79 M | 1 | Hematuria | D/C'd | Recovered |

150.1 Subjects in **Tirofiban group** with serious adverse events **(SAEs) (cont)**

Table 15.0.1.1 SAEs in the tirofiban group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| **TIROFIBAN** | | | | | |
| ***PRISM TRIAL*** | | | | | |
| 011-079 3752 | 84 F | 19 | Angina, unstable | None | Recovered |
| 011-079 3753 | 79 F | 15<br>9 | Pneumonia<br>Heart failure | None | Recovered |
| 011-079 3760 | 69 F | 31 | Angina, unstable | None | Recovered |
| 011-079 3860 | 71 M | 24 | Infection, wound, postoperative | None | Recovered |
| 011-079 3861 | 64 M | 29 | Angina, unstable | None | Recovered |
| 011-079 3862 | 66 F | 12 | Angina, unstable | None | Recovered |
| 011-079 4996 | 47 F | 24 | Angina, unstable | None | Recovered |
| 011-079 4998 | 86 F | 27 | Angina, unstable | None | Recovered |
| 011-079 5026 | 74 M | 29 | Angina, unstable | None | Recovered |
| 011-079 5032 | 66 M | 8<br>8<br>8<br>8<br>8 | Death<br>Heart failure<br>Acidosis<br>Electromechanical dissociation<br>Bleeding, postoperative | None | Death |
| 011-081 6623 | 59 F | 5 | Embolism/infarction, pulmonary | None | Recovered |
| 011-081 6668 | 62 M | 9<br>9 | Shock, cardiogenic<br>Dissection, coronary artery | None | Recovered |
| 011-082 2849 | 67 F | 14<br>14<br>14 | Death<br>Myocardial infarction<br>Shock, cardiogenic | None | Death |
| 011-082 3181 | 67 F | 26 | Pain, musculoskeletal | None | Recovered |
| 011-082 3672 | 61 F | 8 | Angina, unstable | None | Recovered |
| 011-082 5196 | 72 M | 20<br>30 | Angina, unstable<br>Angina, unstable | None | Recovered |
| 011-082 5197 | 62 M | 14 | Angina, unstable | None | Recovered |
| 011-084 3950 | 83 F | 13 | Hypertension | None | Recovered |
| 011-085 3360 | 45 M | 2 | Thrombocytopenia | None | Recovered |
| 011-085 3477 | 65 M | 1 | Thrombocytopenia | D/C'd | Recovered |
| 011-085 3649 | 53 M | 2<br>2 | Cardiac arrest<br>Hypotension | None | Recovered |
| 011-085 3905 | 42 M | 9<br>9 | Death<br>Edema; cerebral | None | Death |
| 011-089 2119 | 69 F | 7<br>4 | Renal insufficiency<br>Peripheral vascular disorder | None | Recovered |
| 011-089 2389 | 55 M | 28<br>1 | Dehiscence, wound<br>Drug overdose | None | Recovered |
| 011-089 2392 | 55 F | 5 | Occlusion, coronary artery | None | Recovered |
| 011-089 2416 | 46 M | 25<br>1 | Angina pectoris<br>Drug overdose | None | Recovered |
| 011-089 2417 | 66M | 11<br>3 | Death<br>Shock, cardiogenic | None | Recovered |
| 011-089 2482 | 70M | 6 | Myocardial infarction | None | Recovered |
| 011-089 2483 | 54 F | 27 | Sarcoidosis | None | Recovered |
| 011-089 7831 | 43 M | 1 | Drug overdose | None | Recovered |
| 011-092 1324 | 72 M | 14 | Angina, unstable | None | Recovered |
| 011-092 1681 | 70 F | 8 | Edema, pulmonary | None | Recovered |
| 011-092 1989 | 55 F | 1 | Hypotension | None | Recovered |
| 011-092 1995 | 69 F | 23 | Gastrointestinal disorder | None | Recovered |
| 011-092 2464 | 66 M | 27 | Angina, unstable | None | Recovered |

15.0.1 Subjects in **Tirofiban** group with serious adverse events **(SAEs) (cont)**

Table 15.0.1.1 SAEs in the tirofiban group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| **TIROFIBAN** | | | | | |
| ***PRISM TRIAL*** | | | | | |
| 011-093 1756 | 70 F | 7<br>7<br>7<br>7 | Death<br>Arrhythmia<br>Cardiac arrest<br>Hypotension | None | Death |
| 011-094 1941 | 71 M | 5<br>5<br>1 | Cardiac arrest<br>Ventricular fibrillation<br>Drug overdose | None | Recovered |
| 011-097 2888 | 77 M | 14 | Angina, unstable | None | Recovered |
| 011-097 3224 | 65 F | 3<br>3<br>3 | Death<br>Edema, pulmonary<br>Trauma, heart | None | Death |
| 011-099 3237 | 64 F | 4 | Shock, cardiogenic | None | Recovered |
| 011-100 3000 | 68 M | 18<br>18 | Death<br>Shock, cardiogenic | None | Death |
| 011-100 3004 | 62 M | 20 | Phlebitis/thrombophlebitis | None | Recovered |
| 011-102 3016 | 84 M | 6<br>5 | Death<br>Shock, cardiogenic | None | Death |
| 011-103 3202 | 68 F | 31<br>30 | Respiratory distress<br>Bleeding, postoperative | None | Recovered |
| 011-103 3213 | 56 M | 1 | Drug overdose | | |
| 011-104 2997 | 70 M | 27 | Cardiac arrest | None | Recovered |
| 011-109 1273 | 79 M | 2<br>30<br>1 | Epistaxis<br>Aneurysm, aortic<br>Drug overdose | D/C'd | Recovered |
| 011-109 2356 | 66 M | 23<br>18 | Pseudoaneurysm<br>Infection, pelvic | None | Recovered |
| 011-113 4152 | 53 F | 10 | Pain, chest | None | Recovered |
| 011-113 4160 | 58 M | 8<br>17 | Angina, unstable<br>Angina, unstable | None | Continuing |
| 011-113 4176 | 80 M | 4 | Heart failure | None | Recovered |
| 011-113 4178 | 68 F | 22<br>9 | Fistula, esophageal<br>Shock, cardiogenic | None | Recovered |
| 011-113 6482 | 59 M | 11 | Mediastinitis | None | Recovered |
| 011-113 6495 | 72 M | 15 | Angina, unstable | None | Recovered |
| 011-113 7314 | 66 F | 17 | Pain, chest | None | Recovered |
| 011-114 3719 | 62 M | 23 | Angina, unstable | None | Recovered |
| 011-114 3726 | 68 M | 22<br>6<br>6<br>6 | Chondrocalcinosis<br>Pseudoaneurysm<br>Bleeding, postoperative<br>Dissection, coronary artery | None | Recovered |
| 011-114 3730 | 75 M | 9 | Occlusion, coronary artery | None | Recovered |
| 011-114 5555 | 76 M | 17<br>17<br>17 | Atrial fibrillation<br>Atrial flutter<br>Pain, chest | None | Recovered |
| 011-114 5597 | 58 M | 2<br>2<br>2<br>1<br>2<br>1 | Death<br>Shock, cardiogenic<br>Cardiac tamponade<br>Cardiomyopathy<br>Heart failure<br>Asystole | None | Death |
| 011-114 5598 | 64 M | 15<br>15 | Pain, abdominal<br>Hyperventilation | None | Recovered |

15.0.1 Subjects in Tirofiban group with serious adverse events **(SAEs) (cont)**

Table 15.0.1.1 SAEs in the tirofiban group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| TIROFIBAN | | | | | |
| *PRISM TRIAL* | | | | | |
| 011-120 5669 | 71 M | 8 | Angina, unstable | None | Recovered |
| 011-120 5713 | 40 M | 9 | Angina, unstable | None | Recovered |
| 011-122 3143 | 70 M | 15 | Angina, unstable | None | Recovered |
| 011-122 3425 | 72 M | 2<br>2<br>2<br>1 | Bradycardia<br>Hypotension<br>Respiratory failure<br>Embolism/infarction, pulmonary | D/C'd | Recovered |
| 011-122 3514 | 66 M | 13<br>13 | Ventricular fibrillation<br>Ventricular fibrillation | None | Recovered |
| 011-122 4806 | 70 F | 28<br>27<br>28<br>28 | Bradycardia<br>Dizziness<br>Hypotension<br>Myocardial infarction | None | Recovered |
| 011-122 4812 | 75 M | 4 | Embolism | None | Recovered |
| 011-122 4815 | 66 F | 24<br>20 | Pneumonia<br>Fracture, vertebra | None | Recovered |
| 011-122 7538 | 85 M | 16 | Drug toxicity | None | Recovered |
| 011-122 7544 | 74 F | 3<br>5 | Cardiac arrest<br>Infection, bacterial | None | Recovered |
| 011-123 3888 | 68 F | 40<br>27<br>27<br>14<br>9<br>9<br>9<br>24<br>9 | Death<br>Pneumonia<br>Renal insufficiency<br>Respiratory insufficiency<br>Heart failure<br>Myelopathy<br>Shock, cardiogenic<br>Shock, cardiogenic<br>Heart failure | None | Death |
| 011-123 4444 | 68 M | 1 | Shock, cardiogenic | D/C'd | Recovered |
| 011-123 4473 | 70 M | 4<br>4 | Hypertensive crisis<br>Edema, pulmonary | None | Recovered |
| 011-123 4668 | 58 M | 13 | Gastritis | None | Recovered |
| 011-125 4524 | 66 M | 14<br>14 | Myocardial infarction<br>Angina, unstable | None | Recovered |
| 011-125 4883 | 69 M | 5 | Angina, unstable | None | Recovered |
| 011-125 4888 | 75 M | 3 | GI hemorrhage, anal/rectal | | |
| 011-125 4894 | 65 F | 24<br>24<br>24 | Syncope<br>Vertigo<br>Fracture, radius | None | Continuing |
| 011-125 5061 | 69 F | 7<br>7<br>7<br>6 | Death<br>Pneumonia<br>Asystole<br>Myocardial infarction | None | Death |
| 011-125 5062 | 75 F | 24<br>24 | Angina pectoris<br>Gastroenteritis | None | Recovered |
| 011-125 5066 | 81 F | 4 | Heart failure | None | Recovered |
| 011-125 5690 | 75 F | 23 | Diverticulitis, intestinal | None | Recovered |
| 011-125 5696 | 77 F | 2 | Herpes zoster | None | Continuing |
| 011-125 5721 | 67 M | 7 | Angina, unstable | None | Recovered |
| 011-127 4542 | 79 F | 17 | Dizziness | None | Recovered |

15.0.1 Subjects in **Tirofiban** group with serious adverse events **(SAEs) (cont)**

Table 15.0.1.1 SAEs in the tirofiban group from the phase III trials *(cont)*.

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| TIROFIBAN | | | | | |
| *PRISM TRIAL* | | | | | |
| 011-127 4543 | 56 M | 7<br>12<br>28 | Hematoma<br>Neoplasm, intestinal, malignant<br>Neoplasm, intestinal, malignant | None | Continuing |
| 011-127 4545 | 42 M | 7 | Myocardial infarction | None | Recovered |
| 011-127 4553 | 46 F | 28<br>2 | Angina pectoris<br>Drug overdose | None | Recovered |
| 011-127 4563 | 59 M | 16 | Angina, unstable | None | Recovered |
| 011-127 4898 | 64 M | 13 | Angina pectoris | None | Recovered |
| 011-127 4900 | 80 F | 4<br>8<br>18<br>25 | Angina, unstable<br>Angina, unstable<br>Angina, unstable<br>Angina, unstable | None | Recovered |
| 011-127 5074 | 80 F | 7<br>6<br>6<br>7 | Atrial fibrillation<br>Edema, pulmonary<br>CVA<br>Pericardium disorder | None | Recovered |
| 011-127 5077 | 67 M | 5 | Infection, postoperative | None | Recovered |
| 011-127 5079 | 65 F | 27 | Effusion, pericardial | None | Recovered |
| 011-127 5354 | 72 F | 3 | Hematoma | None | Recovered |
| 011-129 3134 | 74 F | 17<br>15 | Death<br>Shock, cardiogenic | None | Death |
| 011-132 1341 | 69 F | 21<br>12<br>7<br>2 | Death<br>Hypotension<br>Pneumonia<br>Respiratory failure | None | Death |
| 011-132 2160 62 | 62 M | 30 | Angina, unstable | None | Recovered |
| 011-132 2369 | 80 F | 16 | Pain, musculoskeletal | None | Recovered |
| 011-132 7777 | 48 F | 1 | Drug overdose | None | Recovered |
| 011-132 7852 | 65 F | 20<br>20<br>20 | Nausea<br>Dyspnea<br>Pain, postoperative | None | Recovered |
| 011-133 2253 | 38 M | 27<br>18<br>28 | Angina, unstable<br>Pain, abdominal<br>Myocardial infarction, non-Q-wave | None | Recovered |
| 011-134 1887 | 70 F | 3 | Hemorrhage, gastrointestinal | None | Recovered |
| 011-135 2223 | 80 F | 2 | Edema, pulmonary | D/C'd | Recovered |
| 011-136 2015 | 82 M | 6 | Bronchitis | None | Recovered |
| 011-138 3494 | 79 F | 22 | Bleeding, postoperative | None | Recovered |
| 011-140 4403 | 76 M | 3<br>2 | Death<br>Heart failure | None | Death |
| 011-140 4418 | 68 F | 5<br>5 | Death<br>Cardiac arrest | None | Recovered |
| 011-142 1985 | 83 M | 12 | GI hemorrhage, gastrointestinal | None | Recovered |
| 011-142 2003 | 60 M | 7 | CVA | None | Recovered |
| 011-146 3774 | 71 M | 1 | Hemorrhage, gastrointestinal | D/C'd | Recovered |
| 011-148 3761 | 75 M | 2<br>25 | Drug overdose<br>Angina, unstable | None | Recovered |
| 011-151 4804 | 74 F | 17 | Angina, unstable | None | Recovered |
| 011-152 4793 | 77 F | 1 | Drug overdose | None | Recovered |
| 011-152 5350 | 63 M | 32 | Pericarditis, malignant | None | Continuing |
| 011-152 7439 | 58 F | 7 | Edema, pulmonary | None | Recovered |
| 011-155 4374 | 73 M | 15 | Angina, unstable | None | Recovered |

15.0.1 Subjects in **Tirofiban** group with serious adverse events **(SAEs) (cont)**

Table 15.0.1.1 SAEs in the tirofiban group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| TIROFIBAN | | | | | |
| *PRISM TRIAL* | | | | | |
| 011-155 6552 | 61 M | 4<br>3 | Death<br>Hemorrhage, gastrointestinal | None | Death |
| 011-155 6575 | 75 F | 30 | Heart failure | None | Recovered |
| 011-155 6583 | 44 M | 7 | Bleeding, postoperative | None | Recovered |
| 011-155 6585 | 68 M | 8 | Bleeding, postoperative | None | Recovered |
| 011-155 6706 | 60 M | 12 | Hemiparesis | None | Recovered |
| 011-155 6719 | 58 M | 1 | Drug overdose | None | Recovered |
| 011-155 6795 | 63 M | 11 | Atrial fibrillation | None | Recovered |
| 011-155 6929 | 72 F | 15 | Occlusion, arterial, lower extremity | None | Recovered |
| 011-156 2262 | 84 F | 2 | GI hemorrhage, lower GI | None | Recovered |
| 011-156 7644 | 58 F | 14 | Angina, unstable | None | Recovered |
| 011-157 3458 | 59 F | 2 | AV block, second degree | None | Recovered |
| 011-158 4947 | 55 M | 2<br>2<br>2 | Cardiac arrest<br>Brain damage, anoxic<br>AV block, third degree | D/C'd | Recovered<br>Continuing<br>Recovered |
| 011-160 5128 | 75 M | 22 | Angina, unstable | None | Recovered |
| 011-162 5185 | 46 M | 8 | Angina pectoris | None | Recovered |
| 011-162 5187 | 69 M | 2<br>1 | Death<br>Shock, cardiogenic | None | Death |
| 011-167 2545 | 54 M | 19<br>9 | Postcardiotomy syndrome<br>Hemorrhage, mediastinum | None | Recovered |
| 011-167 7751 | 70 M | 2 | Heart failure | None | Recovered |
| 011-167 7859 | 41 F | 10<br>8 | Death<br>CVA | None | Death |
| 011-167 7861 | 60 M | 2 | Drug overdose | None | Recovered |
| 011-167 7863 | 61 F | 25 | Pain, chest | None | Recovered |
| 011-168 6844 | 59 F | 30 | Angina, unstable | None | Recovered |
| 011-168 6923 | 80 F | 3<br>2<br>2 | Death<br>Cardiac arrest<br>Brain damage, anoxic | None | Death |
| 011-168 6925 | 67 M | 6<br>20 | CVA<br>Days Infection, wound | None | Continuing<br>Recovered |
| 011-168 6987 | 66 F | 20<br>18<br>17 | Death<br>Renal insufficiency<br>Cardiopulmonary failure | None | Death |
| 011-168 6988 | 67 F | 10<br>9 | Effusion, pleural<br>Renal insufficiency | None | Recovered |
| 011-170 6816 | 60 M | 12<br>11 | Death<br>Shock, cardiogenic | None | Death |
| 011-170 6871 | 72 F | 4 | Pseudoaneurysm | None | Recovered |
| 011-171 6759 | 54 M | 22<br>22 | Hypotension<br>Respiratory failure | None | Recovered |
| 011-171 6919 | 61 M | 26 | Ventricular tachycardia | None | Recovered |
| 011-172 6784 | 43 M | 2<br>2 | Death<br>Cardiac arrest | D/C'd | Death |
| 011-172 6845 | 60 F | 15<br>5<br>23 | Pain, chest<br>Angina, unstable<br>Pain, chest | None | Recovered |
| 011-172 6971 | 67 M | 14 | Neoplasm, liver, metastatic | None | Continuing |
| 011-178 7511 | 78 F | 29 | Angina, unstable | None | Continuing |
| 011-178 7516 | 58 M | 17<br>16 | Urinary retention<br>Atrial fibrillation | None | Recovered |

## 15.0.2 Subjects in Tirofiban + Heparin group with serious adverse events (SAEs)

Table 15.0.2.1 SAEs in the tirofiban +heparin group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| TIROFIBAN + HEPARIN | | | | | |
| *PRISM-PLUS TRIAL* | | | | | |
| 006-003 5158 | 59 M | 12 | Angina, unstable | None | Recovered |
| 006-003 5162 | 71 M | 15<br>4 | Ulcer, duodenal<br>Hematocrit decreased | None | Recovered |
| 006-004 5127 | 58 | 28<br>28<br>28 | Septicemia<br>Infection, intra-abdominal<br>Perforation, intestinal | None | Continuing |
| 006-004 5133 | 67 M | 12 | Angina, unstable | None | Recovered |
| 006-008 5144 | 80 M | 7<br>4<br>4<br>4<br>3 | Pneumonia, aspiration<br>Atrial fibrillation<br>Renal insufficiency<br>Heart failure<br>Edema, pulmonary | None | Recovered |
| 006-008 5147 | 69 F | 13 | Reflux esophagitis | None | Recovered |
| 006-010 5174 | 50 M | 28 | Pain, chest | None | Recovered |
| 006-011 5073 | 38 M | 6 | Pain, chest | None | Recovered |
| 006-011 5321 | 49 M | 14 | Angina, unstable | None | Recovered |
| 006-029 6473 | 74 M | 17<br>17 | Death<br>Sudden death | None | Death |
| 006-029 6476 | 53 M | 7<br>3 | Bleeding, postoperative<br>Aneurysm, heart | None | Continuing |
| 006-029 6479 | 47 M | 13 | Angina pectoris | None | Recovered |
| 006-029 6489 | 68 F | 2 | Cerebrovascular accident | None | Recovered |
| 006-033 7110 | 78 F | 30<br>29 | Death<br>Shock, cardiogenic | None | Death |
| 006-034 1023 | 61 F | 19 | Edema, pulmonary | None | Recovered |
| 006-034 1281 | 45 F | 21<br>24 | Angina, unstable<br>Angina, unstable | None | Recovered |
| 006-034 1610 | 81 M | 6 | Death | None | Death |
| | | 6 | Cardiac arrest | None | |
| 006-034 1612 | 63 M | 19 | Angina, unstable | None | Recovered |
| 006-034 1620 | 72 M | 15 | Diverticulitis | None | Recovered |
| 006-034 6009 | 80 M | 16 | Angina, unstable | None | Recovered |
| 006-034 6012 | 64 M | 22<br>22<br>20<br>22 | Pneumonia<br>Bacteremia<br>Postmyocardial infarction syndrome<br>Thrombosis, deep vein | None | Recovered |
| 006-034 6906 | 77 M | 6<br>6<br>6 | Death<br>Ventricular fibrillation<br>Shock, cardiogenic | None | Death |
| 006-034 6934 | 66 F | 11 | Phlebitis/thrombophlebitis | None | Recovered |
| 006-035 1264 | 73 M | 7<br>6<br>6 | Death<br>Heart failure<br>Shock, cardiogenic | None | Death |
| 006-035 1274 | 79 M | 9<br>9 | Death<br>Cardiogenic shock | None | Death |
| 006-035 6378 | 85 F | 18 | Ulcer, gastric with hemorrhage | None | Recovered |
| 006-035 6398 | 79 M | 2 | Hematuria | D/C'd | Recovered |
| 006-035 7355 | 70 F | 1 | Drug overdose | None | Recovered |

## 150.2 Subjects in Tirofiban + Heparin group with serious adverse events (SAEs)

Table 15.0.2.1 SAEs in the tirofiban +heparin group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| TIROFIBAN + HEPARIN | | | | | |
| *PRISM-PLUS TRIAL* | | | | | |
| 006-036 1147 | 75 M | 4<br>4 | Death<br>Ventricular fibrillation | None | Death |
| 006-036 1150 | 85 F | 5<br>5 | Death<br>Heart failure | None | Death |
| 006-036 6184 | 72 M | 19 | Deterioration, general | None | Recovered |
| 006-036 6240 | 79 M | 6 | Hemorrhage, gastrointestinal | None | Recovered |
| 006-036 6263 | 88 F | 14 | Mass, kidney | None | Continuing |
| 006-036 7085 | 89 M | 5 | Bleeding, postoperative | None | Recovered |
| 006-037 1006 | 75 M | 28<br>28 | Heart failure<br>Angina, unstable | None | Recovered |
| 006-037 6053 | 59 F | 14 | Myocardial infarction | None | Recovered |
| 006-037 6073 | 85 F | 9 | Angina, unstable | None | Recovered |
| 006-037 6080 | 69 F | 5<br>5 | Death<br>Shock, cardiogenic | None | Death<br>Recovered |
| 006-037 6990 | 73 M | 91<br>21 | Death<br>Cerebrovascular accident | None | Death<br>Recovered |
| 006-040 1260 | 80 F | 1 | Drug overdose | None | Recovered |
| 006-040 6171 | 47 F | 9<br>1 | Myocardial infarction<br>Drug overdose | None | Recovered |
| 006-040 6846 | 32 F | 1 | Drug overdose | None | Recovered |
| 006-041 1258 | 62 F | 26 | Edema, pulmonary | None | Recovered |
| 006-041 6717 | 94 F | 5<br>4 | Death<br>Shock, cardiogenic | None | Death<br>Recovered |
| 006-041 6721 | 77 M | 20 | Diarrhea | None | Recovered |
| 006-042 6047 | 80 M | 7<br>30<br>30<br>30 | Hematoma<br>Renal insufficiency<br>Chronic obstructive pulmonary disease<br>Angina, unstable | None | Recovered |
| 006-042 6068 | 48 M | 3 | Drug overdose | None | Recovered |
| 006-042 6072 | 76 M | 1 | Drug overdose | None | Recovered |
| 006-042 6962 | 57 M | 13 | Thrombosis, deep vein | None | Recovered |
| 006-043 6362 | 32 F | 20 | Pain, chest | None | Recovered |
| 006-043 6365 | 60 M | 4<br>18 | Asystole<br>Thrombosis, deep vein | None | Recovered |
| 006-043 6679 | 68 F | 1 | Drug overdose | None | Recovered |
| 006-043 6920 | 56 F | 9 | Myocardial infarction | None | Recovered |
| 006-044 1045 | 79 F | 4 | Hemorrhage | None | Recovered |
| 006-044 1070 | 63 M | 22 | Supraventricular tachycardia | None | Recovered |
| 006-044 1072 | 62 M | 4 | Asystole | None | Recovered |
| 006-044 1102 | 72 M | 5 | Surgery, heart vessel, complication | None | Recovered |
| 006-044 1126 | | 9 | Occlusion, coronary artery | None | Recovered |
| 006-044 1343 | 70 F | 23<br>23<br>5<br>23<br>4 | Pain, abdominal<br>Hypertension Moderate<br>Thrombocytopenia<br>Diabetes mellitus<br>Bleeding, postoperative | None | Recovered |
| 006-044 1360 | 69F | 4 | Surgery, heart vessel, complication | None | Recovered |
| 006-044 1361 | 64 M | 4 | Pseudoaneurysm | None | Recovered |
| 006-044 1684 | 69F | 13 | Bradycardia | None | Recovered |

## 15.0.2 Subjects in Tirofiban + Heparin group with serious adverse events (SAEs)

Table 15.0.2.1 SAEs in the tirofiban +heparin group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| TIROFIBAN + HEPARIN | | | | | |
| *PRISM-PLUS TRIAL* | | | | | |
| 006-044 1686 | 80 F | 14<br>14 | Cardiac tamponade<br>Surgery, heart vessel, complication | None | Recovered |
| 006-044 6123 | 58 M | 2<br>1 | Epistaxis<br>Drug overdose | None | Recovered |
| 006-044 6152 | 60 M | 2<br>1 | Drug overdose<br>Drug overdose | None | Recovered |
| 006-044 6196 | 72 M | 1 | Drug overdose | None | Recovered |
| 006-044 6219 | 66 F | 1 | Drug overdose | None | Recovered |
| 006-044 6242 | 67 M | 1 | Pyelonephritis, acute | None | Recovered |
| 006-044 6245 | 71 F | 9 | Neoplasm, intestinal | None | Continuing |
| 006-044 6745 | 62 M | 1 | Drug overdose | None | Recovered |
| 006-044 6750 | 48 M | 1<br>1 | Edema, pulmonary<br>Shock, cardiogenic | None | Recovered |
| 006-044 6756 | 67 F | 26 | Phlebitis/thrombophlebitis | None | Recovered |
| 006-044 6766 | 56 M | 1 | Drug overdose | None | Recovered |
| 006-044 6817 | 73 F | 30 | Edema, pulmonary | None | Recovered |
| 006-044 6822 | 68 F | 8<br>8 | Hematoma<br>Myocardial infarction | None | Recovered |
| 006-044 6824 | 67 M | 15 | Pain, chest | None | Recovered |
| 006-044 6836 | 75 F | 1 | Drug overdose | None | Recovered |
| 006-044 6839 | 73 F | 5 | Pyelonephritis, acute | None | Recovered |
| 006-044 7016 | 64 M | 5 | Reaction, vasovagal | None | Recovered |
| 006-044 7020 | 70 M | 8<br>8 | Death<br>Shock, cardiogenic | None | Death |
| 006-044 7054 | 78 M | 9 | Cerebrovascular accident | None | Continuing |
| 006-044 7061 | 46 M | 10<br>10 | Myocardial infarction<br>Ventricular fibrillation | None | Recovered |
| 006-044 7064 | 68 M | 4 | Drug overdose | None | Recovered |
| 006-044 7078 | 62 F | 28 | Depression | None | Recovered |
| 006-044 7096 | 71 M | 1 | Drug overdose | None | Recovered |
| 006-045 1286 | 62 M | 28 | Obstruction, carotid artery | None | Continuing |
| 006-045 6304 | 56 M | 4 | Occlusion, arterial, lower extremity | None | Recovered |
| 006-047 5152 | 76 M | 14 | Bacteremia | None | Recovered |
| 006-047 5355 | 35 M | 30<br>30 | Cellulitis<br>Heart failure | None | Recovered |
| 006-047 5359 | 69 M | 2<br>2 | Heart failure<br>Bleeding, postoperative | None | Recovered |
| 006-047 5482 | 66 F | 4<br>4 | Pain, chest<br>Atrial fibrillation | None | Recovered |
| 006-047 5520 | 72 F | 4<br>4 | Hemorrhage, gastrointestinal<br>Respiratory failure | D/C'd<br>None | Recovered |
| 006-048 6430 | 64 M | 6<br>6<br>6 | Death<br>Septicemia<br>Shock, cardiogenic | None | Death |
| 006-048-7243 | 77 F | 9<br>5<br>4 | Death<br>Shock, cardiogenic<br>Bleeding, postoperative | None | Death |
| 006-049 6315 | 61 M | 5 | Bronchitis | None | Recovered |

## 15.0.2 Subjects in Tirofiban + Heparin group with serious adverse events (SAEs)

Table 15.0.2.1 SAEs in the tirofiban +heparin group from the phase III trials (cont).

| Protocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| **TIROFIBAN + HEPARIN** | | | | | |
| ***PRISM-PLUS TRIAL*** | | | | | |
| 006-049 6591 | 75 F | 9<br>9<br>9 | Death<br>Ventricular tachycardia<br>Bleeding, postoperative | None | Death |
| 006-050 1034 | 78 F | 3<br>3 | Death<br>Asystole | None | Death |
| 006-050 1623 | 61 F | 29 | Pain, chest | None | Recovered |
| 006-050 6307 | 67 M | 2 | Drug overdose | Interupted | Recovered |
| 006-050 6311 | 34 M | 1 | Drug overdose | None | Recovered |
| 006-050 6699 | 72 M | 29 | Embolism/infarction, pulmonary | None | Recovered |
| 006-050 6978 | 64 F | 17 | Effusion, pleural | None | Recovered |
| 006-053 5096 | 83 F | 1 | Drug overdose | Interupted | Recovered |
| 006-053 5166 | 80 M | 9 | Cerebrovascular accident | None | Recovered |
| 006-053 5268 | 73 M | 12 | Cerebrovascular accident | None | Continuing |
| 006-053 5347 | 72 M | 14 | Heart failure | None | Continuing |
| 006-053 5424 | 74 F | 10 | Lymphoma | None | Continuing |
| 006-055 6849 | 61 F | 5<br>5 | Reaction, vasovagal<br>Bleeding, postoperative | None<br>D/C'd | Recovered |
| 006-056 6411 | 69 F | 5 | Cerebrovascular accident | None | Recovered |
| 006-057 1039 | 48 M | 28<br>10 | Angina, unstable<br>Bleeding, postoperative | None | Recovered |
| 006-057 6111 | 75 F | 6 | Hematoma | None | Recovered |
| 006-057 6332 | 43 M | 20 | Pain, chest | None | Continuing |
| 006-057 6564 | 89 M | 6<br>6 | Death<br>Ventricular arrhythmia | None | Death |
| 006-057 6608 | 56 M | 1 | Drug overdose | None | Recovered |
| 006-057 6610 | 69 M | 11<br>10 | Infection, respiratory<br>Pneumothorax | None | Recovered |
| 006-057 6886 | 55 M | 3 | AV block, third degree | None | Recovered |
| 006-058 6426 | 61 F | 4<br>4 | Ventricular fibrillation<br>Septicemia | None | Recovered |
| 006-058 7383 | 68 M | 11 | Dehiscence, wound | None | Recovered |
| 006-058 7386 | 37 M | 7<br>7<br>15 | Phlebitis/thrombophlebitis<br>Bacteremia<br>Pneumothorax | None | Recovered |
| 006-059 6329<br>006-060 6031 | 43 M | 6<br>2 | Neoplasm, intestinal<br>GI hemorrhage, anal/rectal | None<br>D/C'd | Recovered |
| 006-062 1013 | 72 F | 26<br>25 | Death<br>Angina, unstable | None | Death |
| 006-062 1293 | 77 M | 7<br>5 | Death<br>Edema, pulmonary | None | Death |
| 006-062 6645 | 74 M | 13 | Atrial fibrillation | None | Recovered |
| 006-062 6915 | 70 M | 9<br>11 | Septicemia<br>Renal dysfunction | None | Recovered |
| 006-062 6916 | 60 F | 13<br>2 | Asystole<br>Hours Drug overdose | None | Recovered |

## 15.0.2 Subjects in Tirofiban + Heparin group with serious adverse events (SAEs)

Table 15.0.2.1 SAEs in the tirofiban +heparin group from the phase III trials (cont).

| Protocoll Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| **TIROFIBAN + HEPARIN** | | | | | |
| *PRISM-PLUS TRIAL* | | | | | |
| **006-062 7001** | 74 F | 31<br>7<br>11<br>12 | Death<br>Renal insuffkiency<br>Septicemia<br>Transient ischemic attack | None | Death |
| 006-063 6275 | 46 M | 2<br>3 | Drug overdose<br>Drug overdose | None | Recovered |
| 006-064 6356 | 54 F | 11<br>19 | Pain, leg<br>Phlebitis/thrombophlebitis | None | Recovered |
| 006-064 6359 | 67 M | 10 | Urolithiasis | None | Recovered |
| 006-064 6585 | 70 F | 19 | Pain, chest | None | Recovered |
| 006-064 6953 | 64 M | 1 | Thrombocytopenia | D/C'd | Recovered |
| 006-065 7037 | 65 M | 4 | Dissection, coronary artery | None | Recovered |
| 006-066 5261 | 77 F | 2 | Bacteremia | None | Recovered |
| 006-067 5263 | 67 F | 16 | Infection, wound | None | Recovered |
| 006-067 5288 | 75 M | 10<br>10<br>10<br>9 | Pneumonia<br>Days Respiratory distress<br>Embolism/infarction, pulmonary<br>Cardiovascular hemodynamics abnormal | None | Recovered |
| 006-067 5291 | 75 M | 9 | Neurological disorder | None | Recovered |
| 006-069 5213 | 74 M | 18 | Myocardial infarction | None | Recovered |
| 006-070 5202 | 77 F | 7 | Thrombocytopenia | None | Recovered |
| 006-078 1153 | 57 M | 13 | Otitis media | None | Recovered |
| 006-078 1166 | 81 F | 1 | Drug overdose | None | Recovered |
| 006-078 1707 | 76 F | 9<br>9 | Death<br>Shock, cardiogenic | None | Death |
| 006-078 7466 | 59 M | 12 | Duodenitis | None | Recovered |
| 006-078 7468 | 79 M | 18 | Transient ischemic attack | None | Recovered |
| 006-080 7503 | 75 F | 21 | Gastroenteritis | None | Recovered |
| 006-080 7504 | 63 M | 6 | Sinusitis | None | Recovered |
| 006-080 7723 | 72 F | 9 | Cerebrovascular accident | None | Recovered |
| 006-080 7727 | 48 M | 14 | Myocardial infarction | None | Recovered |
| 006-080 7778 | 71 F | 7 | Angina, unstable | None | Recovered |
| 006-084 1233 | 70 F | 14 | Angina, unstable | None | Recovered |
| 006-084 7514 | 59 M | 28 | Myocardial infarction | None | Recovered |
| 006-084 7652 | 77 M | 2 | Cerebrovascular accident | D/C'd | Recovered |
| 006-084 7660 | 59 F | 22 | Angina, unstable | None | Recovered |
| 006-084 7800 | 59 M | 12<br>12 | Death<br>Rupture, myocardial | None | Death |
| 006-084 7810 | 71 M | 6 | Ventricular fibrillation | None | Recovered |
| 006-084 7821 | 62 F | 26 | Heart failure | None | Recovered |
| 006-085 7509 | 57 M | 4 | Ventricular fibrillation | None | Recovered |
| 006-086 7547 | 48 M | 5 | Bleeding, postoperative | None | Recovered |
| 006-086 7551 | 48 M | 17<br>30 | Angina, unstable<br>Myocardial infarction | None | Recovered |
| **006-086 7553** | 78 M | 2<br>2 | Death<br>Cardiac arrest | None | Death |
| **006-088 7594** | 64 M | 16<br>14<br>3 | Myocardial infarction<br>Angina, unstable<br>Hemorrhage, gastrointestinal | D/C'd | Recovered |

## 15.0.2 Subjects in Tirofiban + Heparin group with serious adverse events (SAEs)

Table 15.0.2.1 SAEs in the tirofiban +heparin group from the phase III trials (cont).

| 'rotocol/ Subject # | Age/ Sex | Day of Onset | Adverse Experience | Action | Outcome |
|---|---|---|---|---|---|
| 'IROFIBAN + HEPARIN | | | | | |
| *'RISM-PLUS* | | | | | |
| )06-089 7632 | 62 F | 21 | Pain, chest | None | Recovered |
| )06-092 7483 | 77 M | 5 | Death | D/C'd | Death |
| | | 5 | Ventricular fibrillation | | |
| | | 5 | Shock, cardiogenic | | |
| )06-092 7644 | 77 F | 10 | Death | None | Death |
| | | 5 | Shock, septic | | |
| | | 5 | Pneumonia | | |
| )06-092 7648 | 54 F | 9 | Death | None | Recovered |
| | | 9 | Shock, cardiogenic | | |
| | | 8 | Surgery, heart vessel, complication | | |
| )06-093 7445 | 53 M | 4 | Hematuria | D/C'd | Recovered |
| )06-093 7453 | 65 M | 7 | Vascular insufficiency, intestinal | None | Continuring |
| | | 3 | Hematuria | D/C'd | Recovered |
| )06-095 1536 | 76M | 7 | Cardiac arrest | None | Death |
| | | 7 | Death | | |
| | | 5 | Renal insufficiency | | |
| | | 7 | Shock, cardiogenic | | |
| )06-095 1539 | 74 F | 16 | Hemorrhage, gastrointestinal | None | Recovered |
| )06-095 1567 | 72 M | 11 | Death | None | Death |
| | | 9 | Heart failure | | |
| | | 11 | Hours Cardiac tamponade | | |
| | | 11 | Hours Cardiac arrest | | |
| | | 11 | Electromechanical dissociation Severe | | |
| )06-096 5245 | 56 F | 7 | Cellulitis | None | Recovered |
| )06-096 5249 | 56 M | 4 | Bleeding, postoperative | None | Recovered |
| )06-102 5500 | 72 F | 3 | Cardiac arrest | None | Recovered |
| )06-102 5501 | 74 M | 17 | Renal insufficiency | None | Recovered |
| | | 17 | Days Respiratory failure | | |
| | | 4 | Hemorrhage, gastrointestinal | | |
| )06-102 5579 | 83 M | 8 | Death | None | Death |
| | | 7 | Heart disorder, ischemic | | |
| | | 7 | Hypotension | | |
| 006-102 5604 | 61 M | 7 | Death | None | Death |
| | | 5 | Renal insufficiency | | |
| | | 5 | Dissection, aortic | | |
| 006-104 5456 | 82 F | 15 | Infection, urinary tract | None | Recovered |
| 006-105 5596 | 78 F | 16 | Effusion, pleural | None | Recovered |
| | | 3 | Asystole | | |
| | | 3 | Cardiovascular hemodynamics abnormal | | |
| 006-107 5553 | 82 M | 15 | Angina, unstable | None | Recovered |
| 006-108 1544 | 82 M | 3 | Asystole | None | Recovered |
| *RESTORE TRIAL* | | | | | |
| 013-002 | M 2 | 33 | Fever | None | Continuing |
| 013-002 1023 | 49 M | 15 | Pain, chest | None | Continuing |
| 013-002 1028 | 74 M | 13 | Pain, chest | None | Recovered |
| 013-002 1798 | 77 M | 6 | Pain, chest | None | Recovered |
| | | 6 | Myocardial infarction | | |
| 013-002 1799 | 61 M | 4 | Ventricular fibrillation | None | Recovered |
| | | 4 | Ventricular tachycardia | | Recovered |
| | | 8 | Fever | | Continuing |
| | | 8 | Infection, skin | | Continuing |